The New England
Journal of Medicine

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Volume 249 JULY 30, 1953 Number 5

PASSIVE IMMUNIZATION IN RELATION TO MULTIPLE CASES OF POLIOMYELITIS IN THE HOUSEHOLD*

Epidemiologic Aspects in New York City, 1949–1952

MORRIS SIEGEL, M.D., M.P.H.† and MORRIS GREENBERG, M.D., M.S.P.H.‡

NEW YORK CITY

THE epidemiologic features of household exposure to poliomyelitis were at first ascertained by the clinical investigations of individual cases[1,2,3] and easily identified population groups in epidemic areas.[8-10] The data indicated that multiple clinical infections in the home were uncommon and, when present, presumably arose simultaneously from the same carrier source or from a member with a subclinical infection. These investigations were subsequently extended to camps, schools and institutions.[11-13] In more recent years, general knowledge has been broadened by the use of laboratory methods, which confirmed the impressions derived from clinical reports and demonstrated that poliomyelitis in the household was accompanied by a high carrier rate among contacts even though multiple clinical infection was uncommon.[14-17] A relation between the occurrence of clinical infection and heredity has been suggested by some investigators.[18,19] The role of still other factors pertaining to the host and the environment have been investigated but, as yet, in a limited way.[5,6,10,20]

In the past year, interest in the effect on household exposure to a clinical case of poliomyelitis was reactivated by the report of the successful application of gamma globulin as a passive immunizing agent in large-scale field tests.[21] The widely publicized results may precipitate an overwhelming public and professional demand for gamma globulin. The critical shortage in supplies, the low incidence of clinical infection, the inability to identify susceptible persons and the limited protective capacity of the biologic product have aroused considerable discussion about its optimum future distribution both in epidemic areas and in the care of contacts.

The current investigation was initiated by the need for data that would serve as a basis for answering some of the questions that have been raised, such as the chances of clinical infection after household exposure, the role of passive immunization in the community control program and the guide lines for the distribution and application of gamma globulin.

METHOD

An analysis was made of the cases of poliomyelitis reported to the Health Department of New York City from 1949 to 1952, inclusive. The clinical and epidemiologic data were obtained by medical inspectors soon after notification.

The minimal diagnostic criteria of clinical poliomyelitis were the presence of fever, stiff neck or back and increased spinal-fluid white-cell count, with or without muscle weakness. Paralytic and nonparalytic cases were included in the study. From 20 to 25 per cent of reported illnesses did not fulfill the full range of diagnostic criteria and were consequently excluded from the Health Department's official roster of cases and from the study.

TABLE 1. *Cases of Poliomyelitis and Deaths, 1949-1952.*

YEAR	NO. OF CASES	CASE RATE per 100,000	NO. OF DEATHS	MORTALITY per 100,000	CASE MORTALITY %
1949	2446	31.0	179	2.2	7.3
1950	1064	13.1	64	0.8	6.0
1951	555	6.8	20	0.2	3.6
1952	821	10.2	28	0.3	3.3

In about 90 per cent of the reported cases the patients were hospitalized within twenty-four hours of diagnosis. The period of hospitalization ranged from several weeks to many months, depending on the needs of the patient. No restrictions were im-

*From the Bureau of Preventable Disease, New York City Department of Health, and the Department of Environmental Medicine and Community Health, State University of New York College of Medicine at New York City.

†Associate professor, Department of Environmental Medicine and Community Health, State University of New York College of Medicine at New York City.

‡Assistant professor of epidemiology, Columbia University College of Physicians and Surgeons; director, Bureau of Preventable Diseases, New York City Department of Health.

posed on household contacts because of the presumed high incidence of carriers in the community.

Table 1 shows the number of cases and deaths reported in New York City between 1949 and 1952. The data indicate that the disease reached epidemic proportions in 1949 and then receded to endemic levels. Previous epidemic outbreaks had been reported for 1916, 1931, 1935 and 1944.[6,8,22]

TABLE 2. *Clinical Types of Poliomyelitis.*

TYPE OF DISEASE	NO. OF CASES	NO. OF DEATHS
Nonparalytic	1902 (38.9%)	0
Spinal paralytic	2163 (44.3%)	38 (1.8%)
Bulbar and bulbospinal	821 (16.8%)	253 (30.8%)
Totals	4886 (100.0%)	291 (6.0%)

The clinical types of poliomyelitis reported during the four-year period under consideration and the case mortality are presented in Table 2.

About 61 per cent of the cases gave evidence of muscular weakness or paralysis. The mortality was largely related to the occurrence of bulbar poliomyelitis, which comprised 16.8 per cent of reported cases.

TABLE 3. *Relation of Age to Clinical Infection.*

AGE	1949 per 100,000	1950 per 100,000	1951 per 100,000	1952 per 100,000
0-4	98.6	45.0	23.2	24.0
5-9	138.8	60.0	30.6	48.5
10-14	91.4	35.8	22.6	31.6
15-24	31.6	14.9	6.9	11.9
25-34	12.3	7.4	2.8	5.4
35-44	3.0	1.5	0.5	1.3
45 and over	0.2	0.3	0.1	0.1
All ages	31.0	13.1	6.8	10.2

The age-specific incidence of clinical infection, based on population estimates in the 1950 census, is shown in Table 3. As had been expected from current trends in New York City, the rates were uniformly highest at five to nine years of age, followed in descending order by ages under four, ten to fourteen and fifteen and over.

Additional information on the conditions of the study and the methods used are described below.

RESULTS

Frequency of Multiple Cases

During the four-year study period, there were 167 households with more than 1 clinical case of poliomyelitis. Of these families, 158 had 2 cases, 7 had 3 cases, and 2 had 4 cases. Table 4 demonstrates the occurrence of multiple cases in the families.*

The yearly percentage of affected families with multiple cases varied from 2.4 to 4.4. The frequency was highest in the epidemic of 1949, when the general incidence was greatest. During the nonepidemic years that followed, the percentages were lower, fluctuating within the narrow range of 2.4 and 3.0. A similar relation between the percentage of families with multiple cases and incidence was reported in New York City for its respective boroughs in 1916,[6] and was also noticed in comparisons made between the epidemics of 1916 and 1931.[8]

The frequency with which 1 or more than 1 case per family occurred can be expressed in absolute terms as a rate per 100,000 households based on the 1950 census (Table 5). The rate for households with multiple cases was about four or five times higher in the 1949 epidemic than in the endemic years of 1950 and 1952. The rates given above indicate that the chances of clinical infection in a household varied from 1 in 1000 to 1 in 5000, and that more than 1 case in the same household might occur in about every 20,000 to 150,000 households.

The annual rates on a household basis reflect the low incidence of the disease and the rarity of multiple cases in the general population under the conditions prevailing in New York City during the study. However, multiple cases occurred in approximately 1 out of 20 to 40 households in which a case of poliomyelitis was reported (Table 5). The ratios, in part, vary with the annual incidence of the disease and consequently might be of some value in measuring epidemicity.

TABLE 4. *Incidence of Multiple Cases.*

YEAR OF ONSET	FAMILIES AFFECTED				
	TOTAL	1 CASE	2 CASES	3 CASES	4 CASES
1949	2338	2235 (95.6%)	98 (4.2%)	5 (0.2%)	0 (—)
1950	1035	1006 (97.2%)	29 (2.8%)	0 (—)	0 (—)
1951	538	522 (97.0%)	15 (2.8%)	1 (0.2%)	0 (—)
1952	797	778 (97.6%)	16 (2.0%)	1 (0.1%)	2 (0.3%)
Totals	4708	4541 (96.4%)	158 (3.4%)	7 (0.2%)	2 (—)

Obviously, the foregoing values also differ significantly with the composition of the family because of the marked differences in age-specific incidence. Some indication of the extent of the difference may be seen from the following estimates based on the

*The terms "family" and "household" are used synonymously to refer to all the persons living in a dwelling, regardless of family relations.

1940 tabulation of household size in New York by the Bureau of Census. By multiplication of the percentage distribution of households with children under eighteen years of age by the total number of households reported in the general population, the size of each category by number of children under eighteen years of age was determined and applied to the data on multiple household infections in the calculation of rates. A summary of the rates by the number of children under eighteen in the household during the four-year study period is presented in Table 6.

There was approximately a ten-fold difference in rates as the number of children under eighteen increased from none to 1 or 2 or more. As expected, the rates varied with the annual incidence in the general population. They were highest in the 1949 epidemic, when multiple cases were reported in about 1 of 6000 households containing 2 or more children under eighteen.

The foregoing data on household incidence were more precisely measured when an age-specific basis of household contacts was made the point of reference. The data were treated in the conventional manner, with reference to the index case as the "initial case" and other cases in the household as "subsequent cases." The cases were not designated as primary or secondary since the source of infection was unknown and often was presumably the same for the household contacts.

A summary of the findings in the 1949 epidemic is given in Table 7. The rates were greatest for those from five to nine years of age and were followed in descending order by the rate at ages under four, ten to fourteen and fifteen to twenty-four and older groups. The order of decreasing magnitude was the same as that observed for the incidence of poliomyelitis in the general population.

The relation of these to the incidence in the general population was studied in terms of both absolute values and the ratio between the rates (Table 8). On the whole, the relative difference was about forty-fold. This paralleled the differences in carrier rates reported for household contacts and others in the general population.[23-25] It should be noted that although the magnitude of the rates followed the same order as that observed in the general population, there was a proportionately greater increase from fifteen to thirty-four years of age than under fifteen. This was reflected in a greater ratio for the older group, particularly among persons twenty-five to thirty-four years of age. It indicates that the increased risk of clinical infection after household exposure was proportionately greater from fifteen to thirty-four years of age than in younger groups.

TABLE 5. *Incidence of Cases per 100,000 Households.*

YEAR	TOTAL	1 CASE	2 CASES	3 CASES	4 CASES	RATE OF MULTIPLE CASES	RATIO OF MULTIPLE CASES TO TOTAL CASES
1949	99.1	94.7	4.2	0.2	0.0	4.4	1:22.7
1950	43.8	42.6	1.2	0.0	0.0	1.2	1:35.7
1951	22.8	22.1	0.6	0.0*	0.0	0.7	1:33.6
1952	33.8	33.0	0.7	0.0*	0.1	0.8	1:41.6

* = 0.04 per 100,000

TABLE 6. *Distribution of Cases among Children under Eighteen Years of Age.*

NO. OF CHILDREN UNDER 18 YR.	DISTRIBUTION OF HOUSEHOLDS IN GENERAL POPULATION	DISTRIBUTION OF HOUSEHOLDS WITH MULTIPLE CASES	ANNUAL RATES PER 100,000 HOUSEHOLDS WITH MULTIPLE CASES		
			1949-52	1949	1950-52
0	53.0	1.2	0.0	0.1	0.0
1	21.9	6.0	0.4	1.4	0.2
2	14.6	42.5	5.2	15.1	1.8
3 or more	10.5	50.3	8.5	17.4	5.5
All households	100.0	100.0	1.8	4.4	0.9

TABLE 7. *Rates of Infection in 1949 Epidemic.*

AGE	NO. OF PERSONS IN HOUSEHOLD	NUMBER AFFECTED INITIALLY	NUMBER NOT AFFECTED INITIALLY	NUMBER SUBSEQUENTLY AFFECTED
yr.				
0-4	1781	686	1095	32 (2.9%)
5-9	1766	747	1019	37 (3.6%)
10-14	1069	398	671	17 (2.5%)
15-24	1174	317	857	13 (1.5%)
25-34	1194	148	1046	9 (0.9%)
35-44	1201	38	1163	0 (—)
45 and over	2351	4	2347	0 (—)
Totals	10,536	2338	8198	108 (1.3%)

Interval between Onsets of Multiple Cases

The interval between the onset of multiple cases in the household was studied in its relation to the

application of passive immunization. The beneficial effects of gamma globulin were said to be limited to a period of five to eight weeks in the dosage prescribed.[28] The prophylactic effects were reported as most marked from the second to the fifth week after inoculation, and much less pronounced or of questionable value after that. In the first week, although the illness was not prevented, the severity of paralysis was reported to be less marked. Under these circumstances, the value of gamma globulin in protecting household contacts depended on how much time elapsed between the administration of gamma globulin and the onset of poliomyelitis.

Reliable data on the date of onset of poliomyelitis may be difficult to assemble because of vague

TABLE 8. *Rates of Infection in General Population and Subsequent Cases.*

AGE	INCIDENCE IN GENERAL POPULATION	INCIDENCE OF "SUBSEQUENT CASES" IN AFFECTED HOUSEHOLDS	RATIO
yr.	*per 100,000 population*	*per 100,000 contacts*	
0–4	98.6	2922.4	30.6
5–9	138.8	3631.0	26.2
10–14	91.4	2533.5	27.7
15–24	31.0	1516.9	48.9
25–34	12.0	860.4	71.7
35–44	2.9	0.0	—
45 and over	0.2	0.0	—
All ages	31.0	1317.4	42.5

prodromal symptoms and the absence of paralysis in about a third of the cases despite laboratory evidence of central-nervous-system involvement. Since changes in the central nervous system are characteristic of poliomyelitis, the onset of the disease in this study was dated from the first appearance of neurologic symptoms. Measurement of the interval between 2 or more cases in a household was therefore based on the time of onset of symptoms of central-nervous-system involvement, such as severe headache, soreness and stiffness of the neck and back, and pain in the extremities.

For purposes of tabulation, the data on the interval between onsets of cases reported in the endemic years of 1950, 1951 and 1952 were combined because the distribution was comparable and the number of cases small. The results are given in Table 9 by daily and weekly interval between the initial case and subsequent cases in the same household. During the crucial period of the first two weeks after the onset of the initial case about 95 per cent of the multiple cases occurred. The cumulative incidence of multiple cases rose rapidly from 10 per cent within twenty-four hours to 52 per cent in less than five days and 63 per cent in the first week. In the second week 33 per cent of the cases occurred, making the total 96 per cent in the first two weeks. The few cases that occurred after that were distributed between the third and fifth weeks. No cases occurred after the fifth week, since the longest interval between the first and all other subsequent cases in the family was thirty-one days.

Thus, only about a third of the cases developed in the second to fifth weeks, when gamma globulin is said to be most effective, and almost two thirds occurred in the first week, before any measure for passive immunization had time to prevent the onset of the disease. The same concentration of cases in the first two weeks was seen in the epidemic and endemic years under consideration. Since none of the multiple cases occurred after the fifth week, there seemed to be no need of protective measures among household contacts after this period.

The constancy of the foregoing observations was checked with past experience in New York City and elsewhere. In New York City the results ob-

TABLE 9. *Distribution of Multiple Cases in Household by Interval between Onsets of Cases.*

INTERVAL	NO. OF CASES		TOTAL CASES	CUMULATIVE INCIDENCE
	1949	1950–1952		NO. OF CASES
days				
0	9	9	18 (10.1%)	18 (10.1%)
1	7	4	11 (6.2%)	29 (16.3%)
2	13	10	23 (12.9%)	52 (29.2%)
3	17	8	25 (14.0%)	77 (43.2%)
4	12	4	16 (9.0%)	93 (52.2%)
5	6	5	11 (6.2%)	104 (58.4%)
6	2	6	8 (4.5%)	112 (62.9%)
7	5	6	11 (6.2%)	123 (69.1%)
8	8	2	10 (5.6%)	133 (74.7%)
9	5	3	8 (4.5%)	141 (79.2%)
10	8	2	10 (5.6%)	151 (84.8%)
11	2	3	5 (2.8%)	156 (87.6%)
12	6	2	8 (4.5%)	164 (92.1%)
13	4	2	6 (3.4%)	170 (95.5%)
14–20	2	0	2 (1.1%)	172 (96.6%)
21–27	2	3	5 (2.8%)	177 (99.4%)
28–34	0	1	1 (0.6%)	178 (100.0%)
Totals	108	70	178	

tained from 1949 to 1952 were compared with those reported in the outbreaks of 1916[6] and 1931,[5] when the information on multiple cases was carefully documented. About 72 per cent of the cases occurred in the first week, 22 per cent in the second week, 5 per cent in the third to fifth weeks, and 1 per cent after the fifth week (Table 10). In the first two weeks, therefore, from 93 to 96 per cent of the cases were found. An early concentration of cases was also observed in Sweden in 1905,[8] in Massachusetts in 1916 and elsewhere in the United States from 1921 to 1924.[7]

Consequently, the elapsed time between the onset of multiple cases in a household followed a uniform pattern. It appears to be a serious limitation to the applicability of passive immunization in familial contacts. Any delay in diagnosis or inoculation of gamma globulin would obviously reduce its value still further. Reinoculations to prolong passive

immunity among intimate contacts seem to be unnecessary under the foregoing conditions.

Associated Factors

Since the time factor is important in the application of passive immunization, the relation of the interval between the initial and subsequent cases to such factors as age and clinical manifestations was studied. The distribution of subsequent cases by age is given in Table 11.

There was a progressive increase in the incidence of subsequent cases occurring after the first week from 32 per cent under four years of age to 42.9 per cent at twenty-five to thirty-four or 50 per cent at twenty-five to forty-four. From this it seems that passive immunization would be somewhat more effective in older contacts than in younger. However, the difference did not seem great enough to compensate for the lower incidence of clinical infection over fourteen years of age in deciding which group would benefit most from the use of the limited supply of gamma globulin.

On the other hand, the importance of protecting household contacts over fifteen years of age becomes more apparent when the severity of infection as determined by mortality is considered. A summary of the death rates per 100,000 household contacts observed in 1949 is presented in Table 12. The death rate was about twice as high at fifteen to thirty-four years of age as under fifteen. Over thirty-four years of age, there were no cases in the small group under consideration in 1949.

Mortality was related to age and frequency of bulbar poliomyelitis regardless of time of onset in the household. A summary of the case mortality in multiple household infections observed during the study period and referred to as "subsequent cases" is given in Table 13.

The case mortality was 4.2 per cent in the group under fifteen years of age and 30.6 per cent in the group fifteen years and over. The mortality was 46.7 per cent in the bulbar and 4.2 per cent in the spinal cases. Bulbar poliomyelitis seemed to be particularly serious in persons over fifteen years of age, for all the 10 patients with bulbar cases in this age group died as against 4 deaths in 20 cases among younger patients.

The increased severity of poliomyelitis over fifteen years of age conforms to the pattern generally observed.[27] It was reflected in a higher case mortality in these patients than in younger ones. The relation of mortality to incidence by age in the general population of New York City is summarized in Table 14. The mortality rates varied with incidence. However, they were proportionately higher in patients over fifteen than in those under fifteen years of age, as shown by the ratio of mortality to incidence, which was about three times larger in the former than in the latter. Since the incidence dwindled markedly among persons thirty-five years of age and over, there was a sharp drop in the mortality rate of this group. Under that age, the mortality rates were relatively high, being highest at five to nine years of age.

From the foregoing it seems that protective measures are needed for a broad age group because of high incidence or mortality. Under fifteen years of age, the need for protection is generally recognized largely because of elevated incidence; from fifteen to thirty-four it might also be essential in the reduction of mortality.

TABLE 10 *Interval between Onsets of Multiple Cases in New York City, (1916, 1931, 1949, 1950-52).*

INTERVAL wk.	TOTAL	1950-52	No. OF CASES 1949	1931	1916
1	496 (72.1%)	46 (65.7%)	66 (61.1%)	73 (70.9%)	311 (76.4%)
2	150 (21.8%)	20 (28.6%)	38 (35.2%)	23 (22.3%)	69 (16.9%)
3-5	33 (4.8%)	4 (5.7%)	4 (3.7%)	6 (5.8%)	19* (4.7%)
6 and over	9 (1.3%)	0 (—)	0 (—)	1 (1.0%)	8* (2.0%)
Totals	688 (100%)	70 (100%)	108 (100%)	103 (100%)	407 (100%)

*Estimates.

TABLE 11. *Interval between Onsets of Initial and Subsequent Cases.*

AGE yr.	TOTAL CASES	INTERVAL OF 1 WK. NO. OF CASES	INTERVAL OF 2 TO 5 WK. NO. OF CASES	INCIDENCE OF TOTAL CASES AFTER 1 WK. %
0-4	47	32 (28.6%)	15 (22.7%)	32.0
5-9	64	41 (36.6%)	23 (34.9%)	36.0
10-14	31	19 (17.0%)	12 (18.2%)	38.7
15-24	20	12 (10.7%)	8 (12.1%)	40.0
25-34	14	8 (7.1%)	6 (9.1%)	42.9
35-44	2	0 (—)	2 (3.0%)	—
All ages	178	112 (100.0%)	66 (100.0%)	36.0

TABLE 12. *Deaths among Household Contacts (1949).*

AGE yr.	No. OF DEATHS	DEATH RATE per 100,000 contacts
All ages	13	158.6
Under 15	5	179.5
15-34	8	420.3

Discussion

The study described above was undertaken largely for the purpose of obtaining local data that could be used in answering some of the questions about the most effective application of passive immunization. In the course of the study some interesting epidemiologic relations became apparent and were investigated.

The scope of the investigation was limited largely to an analysis of multiple household cases to determine the presumptive conditions under which passive immunization might best be applied in an effort to protect family members exposed to clinical household infection. Two broad aspects of the problem were investigated: one concerned incidence, and the other the interval between onset of initial and subsequent cases.

Several points of interest are to be noted in the incidence. In the first place the frequency of multiple infections varied with annual incidence and number of household members under eighteen years of age. Thus, it was related to epidemicity and number of susceptible persons intimately exposed.

Secondly, there was a forty-fold difference in incidence between familial contacts and the general population. The extent of the difference between these two groups paralleled that reported by others for fecal carriers.[23-25] In other words, there was an association among degree of exposure, carrier rate and clinical infection.

Thirdly, there was a proportionately greater increase in clinical infection among household contacts from fifteen to thirty-four years old than for those under fifteen years of age. These differences could have been due to a number of factors, artificial or real. These include the possibility of underreporting of cases in the older age groups, the question of a truly greater susceptibility of these age groups to clinical infection after exposure in the household, a difference in incubation period and a greater proportion of subclinical infection in the younger age groups. At the least these data indicate the need for protecting the older contacts in the age group fifteen to thirty-four as well as those under fifteen. Additional evidence to support the need for protecting older contacts was an increased frequency of bulbar poliomyelitis and a higher case mortality. Obviously, these results refer to the conditions prevailing in the study. Under other conditions and in other areas the age span needing protection may be different.[28-30]

Table 13. *Case Mortality in Multiple Household Infections.*

Clinical Type of Poliomyelitis	Patients under 15 Yr. of Age			Patients 15 Yr. of Age and over		
	No. of Cases	No. of Deaths	Case Mortality %	No. of Cases	No. of Deaths	Case Mortality %
Nonparalytic	70	0	0.0	7	0	0.0
Spinal paralytic	52	2	3.8	19	1	5.3
Bulbar	20	4	20.0	10	10	100.0
Totals	142	6		36	11	
Averages			4.2			30.6

Table 14. *Average Annual Age-Specific Incidence and Mortality (1949-1952).*

Age	Average Rate		Mortality-Incidence Ratio
	Incidence per 100,000 population	Mortality per 100,000 population	
yr.			
0–4	48.5	1.4	2.9
5–9	69.5	3.1	4.5
10–14	45.4	2.1	4.6
15–24	16.3	1.8	11.0
25–34	7.0	1.0	14.3
35–44	1.6	0.2	13.6
45 and over	0.2	0.0	—
All ages	15.3	0.9	5.9

The data on the interval between the onset of the first and subsequent cases confirmed past observations on the concentration of household cases within a short span of time in which about 95 per cent occurred in the first two weeks.[5-10] The close grouping of household cases in the first week appears to be a serious limitation to the usefulness of passive immunization and makes the early diagnosis and administration of gamma globulin imperative.

Two interesting observations were made concerning the interval between initial and subsequent cases in the household. The first was that there appeared to be an increase in the percentage of "subsequent" cases developing after the first week of the initial case as the age of the patient in the subsequent case rose. Although the differences were not great, they were consistent and were indicative of a longer incubation period, which suggests the possibility that a larger number of older than younger contacts could be helped by passive protection.

Secondly, from 99 to 100 per cent of the household cases occurred within five weeks. In other words, those who were going to contract clinical infection after household exposure did so during the incu-

bation period of the disease. This coincides with the duration of protection afforded by a single inoculation of gamma globulin and makes reinoculation unnecessary.

Despite the limitations of passive immunization of household contacts, the expected modification of severity and reduction of incidence should reduce the mortality rate even if only a few contacts are benefited.

Summary

The epidemiology of multiple household infections occurring in New York City from 1949 to 1952 was studied with particular reference to the applicability of passive immunization as a community control measure.

The percentage of households affected with more than one case of poliomyelitis in a given year varied with the annual incidence of 2.4 to 4.4.

The incidence of multiple household infections was related to the number of household members under eighteen years of age and to the annual attack rate in the general population.

The time interval between the onset of the initial and subsequent cases in a household followed a characteristic pattern, most of the cases occurring within the first week, about 95 per cent within two weeks, and 99 to 100 per cent within five weeks. The percentage of cases after the first week seemed to be somewhat higher among persons fifteen to thirty-four than among those under fifteen years of age.

The incidence of poliomyelitis in household contacts after the onset of the index case was about forty times greater than that of the general population. It was proportionately greater at fifteen to thirty-four than below fourteen years of age. In the group from fifteen to thirty-four, the frequency of bulbar poliomyelitis and the mortality were also increased.

We are indebted to Miss Helen E. Solomon for her assistance in compiling the data.

References

1. Pasteur, W. Epidemic of infantile paralysis occurring in children of same family. *Tr. Clin. Soc. London* **30**:143-150, 1897.
2. Packard, F. A. Acute anterior poliomyelitis occurring simultaneously in brother and sister; with remarks upon its etiology. *J. Nerv. & Ment. Dis.* **26**:210-216, 1899. (Discussion, pp. 240-242.)
3. Sutherland, C. R., and Robinson, W. Two cases of poliomyelitis in one house. *Lancet* **2**:1083, 1910.
4. Wilkinson, K. D. Three cases of acute anterior poliomyelitis in one family. *Brit. M. J.* **2**:1017, 1911.
5. Wickman, I. *Acute Poliomyelitis (Heine-Medin's Disease)*. 135 pp. Nervous and Mental Disease Monograph Series, No. 16. New York: The Journal of Nervous and Mental Disease Publishing Co., 1913.
6. Lavinder, C. H., Freeman, A. W., and Frost, W. H. *Epidemiologic Studies of Poliomyelitis in New York City and the Northeastern United States during the Year 1916. Pub. Health Bulletin, No. 91.* 310 pp. Washington, D. C.: U. S. Public Health Service, 1918.
7. Aycock, G. F., and Eaton, P. Epidemiology of infantile paralysis: relation between multiple cases in same family. *Am. J. Hyg.* **5**: 724-732, 1925.
8. Best, W. H. Unpublished data.
9. International Committee for the Study of Infantile Paralysis. *Poliomyelitis*. 562 pp. Baltimore: Williams and Wilkins Co., 1932.
10. McFarlan, A. M., Dick, G. W. A., and Seddon, H. J. Epidemiology of 1945 outbreak of poliomyelitis in Mauritius. *Quart. J. Med.* **15**: 183-208, 1946.
11. Kramer, S. D., Gilliam, A. G., and Molner, J. G. Recovery of virus of poliomyelitis from stools of healthy contacts in institutional outbreak. *Pub. Health Rep.* **54**:1914-1922, 1939.
12. Silverman, A. C. Institutional outbreak of poliomyelitis. *Am. J. Pub. Health* **31**:593-598, 1941.
13. Ingalls, T. H., and Rubenstein, A. D. Expectancy for outbreaks of poliomyelitis in camps and schools. *Am. J. Pub. Health* **40**:555-560, 1950.
14. Langmuir, A. D. Carriers and abortive cases in rural poliomyelitis outbreak. *Am. J. Pub. Health* **32**:275-281, 1942.
15. Zintek, A. R. Rapid infection of family after introduction of poliomyelitis virus. *Am. J. Hyg.* **46**:248-253, 1947.
16. Wenner, H. A., and Tanner, W. A. Widespread distribution of poliomyelitis in households attacked by disease. *Proc. Soc. Exper. Biol. & Med.* **66**:92-94, 1947.
17. Brown, G. C., Francis, T., Jr., and Ainslie, J. Studies of distribution of poliomyelitis virus: virus in familial associates of cases. *J. Exper. Med.* **87**:21-27, 1948.
18. Aycock, W. L. Familial aggregation in poliomyelitis. *Am. J. M. Sc.* **203**:452-465, 1942.
19. Herndon, C. N., and Jennings, R. G. Twin-family study of susceptibility to poliomyelitis. *Am. J. Human Genet.* **3**:17-46, 1951.
20. Seddon, H. J., Agius, T., Bernstein, H. G. G., and Tunbridge, R. E. Poliomyelitis epidemic in Malta 1942-43. *Quart. J. Med.* **14**:1-26, 1945.
21. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., Klimt, C. R., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 3. Preliminary report of results based on clinical diagnosis. *J. A. M. A.* **150**:757-760, 1952.
22. Greenberg, M., Siegel, M., and Magee, M. C. Poliomyelitis in New York City, 1949. *New York State J. Med.* **50**:1119-1123, 1950.
23. Pearson, H. E., Brown, G. C., Rendtorff, R. C., Ridenour, G. M., and Francis, T., Jr. Studies of distribution of poliomyelitis virus in urban area during epidemic. *Am. J. Hyg.* **41**:188-210, 1945.
24. Casey, A. E., Fishbein, W., Schabel, F. M., Jr., and Smith, H. T. Incidence of subclinical poliomyelitis in urban area according to age groups. *Am. J. Pub. Health* **40**:1241-1250, 1950.
25. Francis, T., Jr. Distribution of poliomyelitis virus in epidemic community. *Tr. A. Am. Physicians* **65**:176-183, 1952.
26. Hammon, W. McD., Coriell, L. L., Wehrle, P. F., and Stokes, J., Jr. Evaluation of Red Cross gamma globulin as prophylactic agent for poliomyelitis. 4. Final report of results based on clinical diagnoses. *J. A. M. A.* **151**:1272-1285, 1953.
27. Lenhard, R. E. Prognosis in poliomyelitis. *J. Bone & Joint Surg.* **32-A**:71-79, 1950.
28. Adamson, J. D., et al. Poliomyelitis in Arctic. *Canad. M. A. J.* **61**: 339-348, 1949.
29. Peart, A. F. W. Outbreak of poliomyelitis in Canadian Eskimos in wintertime, epidemiological features. *Canad. J. Pub. Health* **40**: 405-417, 1949.
30. Paul, J. R. Geography and antibodies. *Tr. A. Am. Physicians* **65**: 184-190, 1952.

FURTHER OBSERVATIONS ON MENTAL DISTURBANCES ASSOCIATED WITH CORTISONE AND ACTH THERAPY*

LINCOLN D. CLARK, M. D.,† GARDNER C. QUARTON, M. D.,† STANLEY COBB, M. D.,‡ AND WALTER BAUER, M.D.§

BOSTON

A PREVIOUS paper described in detail the clinical and laboratory aspects of 10 cases in which mental disturbances of varying severity developed during treatment with cortisone or ACTH.[1] The primary intention of that report was to characterize the natural history and symptomatology of this syndrome. To give a more exact description, cases that failed to demonstrate a clear relation between hormone administration and the occurrence of psychiatric complications were excluded. For example, none had a past history of overt psychiatric illness or nervous-system disease, none had known endocrinologic dysfunction, and none coincidentally received nonhormonal drugs or suffered metabolic dyscrasias to which a "toxic" psychosis might be ascribed. All the patients who manifested major mental disturbances suffered from either rheumatoid arthritis (5 cases) or disseminated lupus erythematosus (1 case).

The group of patients described below is more diverse, including those with a past history of psychiatric breakdown, with underlying nervous-system disease or with a known endocrinopathy. In all cases the psychiatric complications were of major severity. They represent the incidence of such complications occurring in the Massachusetts General Hospital since the writing of the previous report. In contrast to the cases in that report and to most of the series described in the literature, many of these patients were not treated for diseases of the connective-tissue group or of "psychosomatic" character.

The mechanisms by which these disturbances occur and the factors involved in individual susceptibility to them remain obscure; unfortunately, this paper will not shed any fundamental light on this obscurity. Rather, these case reports are presented, first, to amplify further the clinical syndrome of hormonal psychosis, secondly, to exemplify some of the difficulties involved in interpreting mental disturbances that arise during hormonal therapy and, finally, to suggest, in several of the cases, some of the factors that may be related to individual susceptibility. It is believed that these reports and the subsequent discussion will be of practical value to those managing patients under cortisone or ACTH therapy, as well as an addition to collective experience with this problem.

In a subsequent paper,[2] an extensive review of the literature concerning ACTH and cortisone psychosis will be reported, with an analysis of the numerous conceptual schemes within which these disturbances may be interpreted. Discussion of the more theoretical aspects of this problem will accordingly be reserved for that paper.

The first cases to be presented, like those in the previous report, were relatively uncomplicated. The remainder demonstrated a greater complexity of factors of possible relevance to the interpretation and the occurrence of the mental disturbance that arose during therapy.

CASE REPORTS

CASE 1. A. B. (M. G. H. 688537), a 49-year-old woman, received 3200 mg. of ACTH intramuscularly, over the course of 33 days, for the treatment of moderately advanced Paget's disease. Before therapy, a psychiatrist described her as a "fairly anxious, somewhat excitable woman" but "essentially normal." There was no demonstrable effect on the bone disease, but 30 days after the onset of therapy she was depressed and tearful. She became increasingly depressed and agitated during the next few days. She believed that the hair on her lip that had appeared during ACTH therapy would become a permanent moustache, and she would not accept reassurance to the contrary. Within 1 week complete recovery occurred, and she has remained well from a psychiatric standpoint.

An electroencephalogram taken early in the course of the mental disturbance revealed diffuse, bilateral slow-wave activity. The tracing reverted to normal with clinical recovery.

Case 2. H. C. (M.G.H. 688876), a 42-year-old woman, during a period of 1 year, received 3 courses of ACTH and 1 of cortisone in treatment of pemphigus vulgaris without psychiatric complications. She was a chronically insecure, emotionally labile woman who had adjusted herself remarkably well to a 20-year sequence of personal and family misfortunes of disturbing proportions.

Her fourth course of ACTH consisted of 2600 mg. given intravenously during 27 days. The last dose was administered on May 15, 1951. Her course was uneventful until the last week of therapy, when she was observed to be unusually quiet, seclusive and unjustifiably irritable with fellow patients. However, these changes were not considered sufficiently remarkable to postpone discharge.

Seven days later she and her husband were seen in the Outpatient Clinic, and the husband reported "peculiar" behavior during the interval since discharge. He described severe insomnia, restlessness, distractibility, lability of mood, press of speech and the performance of impulsive, irrational acts. She put her hair curlers in the ice box. She had walked from a changing booth into the main section of a store clothed only in her slip. During a visit to her mother-in-law's grave she displayed intense grief whereas on the occasion of the death 6

*From the Medical and Psychiatric Services, Massachusetts General Hospital, and the departments of Medicine and Psychiatry, Harvard Medical School.

Publication No. 146 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Disease, Harvard Medical School. The expenses of this investigation were defrayed in part by grants from the Commonwealth Fund and the United States Public Health Service.

†Assistant in psychiatry, Harvard Medical School and Massachusetts General Hospital.

‡Bullard Professor of Neuropathology, Harvard Medical School; psychiatrist-in-chief, Massachusetts General Hospital.

§Jackson Professor of Clinical Medicine, Harvard Medical School; chief, Medical Services, Massachusetts General Hospital.

months before she had "held in her feelings." No delusions or hallucinations were present.

Improvement occurred over the next month.

On September 26 she was readmitted to the hospital with a relapse of the pemphigus and received 580 mg. of ACTH intravenously over a course of 28 days without complications. She was again admitted on April 20, 1952, with herpes simplex and urticaria. She was anxious and frightened, fearing a relapse of pemphigus, but no inappropriate behavior was observed.

CASE 3. F. B. (M. G. H. 695876), a 41-year-old woman, was admitted to the hospital on January 11, 1951, for further treatment of generalized lymphocytic lymphoma. She had no history of psychiatric illness; she had received a previous course of ACTH, 2565 mg. in 30 days, without mental symptoms. Cortisone was given from March 3 to March 13. She received a total of 1300 mg. Her course was uneventful until March 12, when marked press of speech and exhilaration were noted. She then developed ideas of reference, believing that the ward nurse was "psychoanalyzing" her because a desk lamp pointed in her direction. She had auditory illusions of paranoid-depressive character. She was unable to keep track of time and thought that her memory was defective.

Her mental disturbance continued with a markedly varied course. At times she was quite lucid; at others she was paranoid, with auditory illusions and hallucinations. For a time she was in a state resembling catatonic stupor, immobile, mute and negativistic, and *flexibilitas cerea* was demonstrable. Her speech returned, with punning and echolalia. In answer to questions she intoned "ring-rang" as if she were a bell. She showed posturing, grimacing and staring reactions, and later, overactivity and assaultiveness. She gradually improved, passing again through a period in which she described her depressive delusions. Lucid periods occurred with increasing frequency, interrupted by periods of hallucinations, inappropriate affect and poorly structured paranoid delusions. By May 13 her mental state had returned to normal.

After discharge she remained free of further mental symptoms although her lymphoma became worse and she received x-ray therapy.

CASE 4. E. R. (M. G. H. 744839), a 63-year-old, Italian-born tailor, had been admitted to the hospital 3 times for treatment of pemphigus foliaceus (chronic benign pemphigus). One course of ACTH consisted of 20 mg. intravenously a day for 25 days and a second, a month later, of 30 mg. daily for 30 days. Each time his skin improved, but with a relapse at the end of treatment. He was apprehensive over the course of his disease, but no psychiatric changes were noted other than mild euphoria. Although he was maintained for three months on 20 to 40 mg. of ACTH intravenously 3 times a week after his 2d discharge, his skin became worse, and he returned to the hospital on September 9, 1952. He received 40 mg. of ACTH a day. This was gradually increased at weekly intervals to a maximum of 240 mg. a day. He received a total of 7947 mg. in 63 days.

Before the 3d course of therapy the patient seemed discouraged over his chronic relapsing disease and because his wife had recently been admitted to a mental hospital with an involutional depression. He missed her support and thought that his illness might have led to her depression. He had started as a poor immigrant and owned a successful tailoring shop in an academic community. He feared that unless his face was free of lesions his customers would find him repulsive. He believed that his pemphigus was caused by penicillin given by a physician for an incidental illness before his skin disease. He denied resentment over what he regarded as a catastrophic mistake. He was pleasant, ingratiating and slightly condescending, expressing confidence in the doctors at the same time that he hinted that they could have prevented his relapses.

On September 25 he complained of heaviness or "fuzziness" in his head and feelings of detachment, and talked gallantly but unconvincingly of his fear of death. Later, he openly expressed his lack of confidence in the doctors. He spoke of making a will and hinted at suicide. On one occasion he was found in an intensely agitated state, tying bed sheets about his arms in a futile effort to "cut off circulation." Reassurance was ineffective. Later, after the dosage had been increased to 160 mg. a day, he alleged that the doctors planned to exsanguinate him. He treated this with pseudocomposure. The delusions disappeared when the dose was dropped to 80 mg. and returned with resumption of the previous level. One day after the dose was raised to 240 mg. he suffered paranoid auditory hallucinations. He believed that he was being poisoned and that God had confided to him a solution of the Korean situation.

From November 5 the dose was reduced from 280 mg. to 0 at the rate of 30 mg. a day. After withdrawal there were signs of hypoadrenalism, with unstable blood pressure, tachycardia, fever of unknown origin, weakness, apathy and semistupor. Then the patient improved mentally as well as physically. Recovery was complete at the time of discharge on December 24, when the skin disease was also in complete remission. His wife was released from the mental hospital on the same day. Both have settled down to their usual pattern of life.

CASE 5. C. T. (M. G. H. 743520), a 23-year-old married woman, was admitted to the hospital for treatment of an exacerbation of disseminated lupus erythematosus. The disease had begun when she was 21 and had required 2 previous hospitalizations, during 1 of which she received 5950 mg. of cortisone over 59 days without obvious mental symptoms.

The patient's father had died when she was a small child, and she had always been in conflict with her mother, who resented her marriage. Several physicians noted that her disease was worse when there were violent quarrels between her mother and her husband.

On admission, she was severely ill, with a temperature of 104°F., epistaxis, a sore throat, joint pains and extensive skin involvement. Because of the severity of the disease she was treated with 500 mg. of cortisone for the first 2 days, 300 mg. for the 3d and 4th days and 200 mg. for the next 2 days. At the same time that there was marked improvement of her general condition, she became apprehensive and depressed, with fear of loss of control, sudden dislikes of certain persons and tight sensations in the head. She became retarded, with suicidal ideas, and expressed a belief that the nurses hated her.

When cortisone was stopped there was a moderate improvement, but when it was started again for 9 days at an average daily dose of 180 mg., she became much more paranoid. At the same time, bilateral extension plantar reflexes were found; the spinal fluid protein was elevated, and somewhat later she suffered 4 generalized convulsions. After the convulsions, she was even more paranoid, negativistic and depressed, but she then showed confusion in addition. Her general condition deteriorated and she died on the 59th hospital day.

CASE 6. A. P. (M. G. H. 98025), a 25-year-old married man, was admitted to the hospital for treatment of an extremely severe rheumatic fever with rheumatic heart disease and congestive heart failure. He had suffered episodes of rheumatic fever at 8 and 13 years of age. When he was 8 his sister died of heart disease on the day of her wedding. As a result he was frightened, but in his adolescence he manifested an extreme, defiant independent attitude. He became a successful draftsman and married.

At the time of admission he was extremely ill. On the 6th hospital day, when his temperature was 103°F. and he was receiving a salicylate, theobromine calcium, ammonium chloride and prophylactic penicillin therapy, a mental disturbance developed, lasting 3 days and characterized by anxiety, flight of ideas, confusion and peculiar impulses, such as wanting to hurt the nurses who helped him most.

Because of the gravity of his medical condition, the decision was made to give him cortisone. A total dose of 1350 mg. was given in 12 days, the daily dosage ranging from 25 to 300 mg. On the day it was started he was again slightly disoriented. Electrolyte findings (potassium of 7.0 milliequiv. and carbon dioxide of 19.3 milliequiv. per liter and nonprotein nitrogen of 43 mg. per 100 cc.) were consistent with prerenal azotemia and acidosis, aggravated by ammonium chloride therapy. During the first 5 days of treatment, he improved dramatically, becoming afebrile and subjectively quite well. On the 9th day of cortisone therapy, however, he became excited, confused and deluded, with vivid frightening hallucinations. He believed that movies were being taken of him and that a ring of butchers were trying to get him. Cortisone was stopped at the height of the disturbance, and he recovered in 6 days. Subsequently, he did well in every respect.

CASE 7. S. S. (M. G. H. 744835), a 52-year-old single woman, was admitted to the hospital for treatment of a generalized exfoliative dermatitis. There was a history of mild diabetes and of anginal pain. The dermatitis had begun 1 month before

admission during the course of a febrile illness diagnosed as pneumonia at another hospital. She had received an unknown amount of ACTH, without improvement. Symptoms of weakness, generalized joint pain on movement and conjunctivitis developed.

The patient was the only unmarried sibling in a close Jewish family of 10 children. She was solitary, self-effacing and ingratiating, and never showed anger to anyone. She exhausted her savings. There was no known family history of mental disease.

She was treated conservatively for 15 days without benefit. The diabetes was controlled without difficulty. She was found to have a nonprotein nitrogen of 62 mg. per 100 cc. and was anemic.

She was then given 20 mg. of ACTH intravenously for 10 days. On the 3d day of treatment she became depressed, refused food, and had crying spells, but there was no confusion or delusional thinking. She improved after 4 days even though ACTH was continued. Her skin improved. On the 9th day of treatment, she suddenly became extremely confused and disoriented concerning time and place, but was not depressed. Because of this episode, ACTH was stopped, and her condition returned to normal except for slight euphoria. Three days later she again became severely depressed and retarded, with mutism, negativism and depressive delusional thinking. She said, "Why do you torture a dead person so?" As far as could be determined she was oriented during this episode, which cleared suddenly after 4 days. She remained without psychiatric symptoms for 25 days of hospitalization and until her sudden death from myocardial infarction 4 months later.

The mental symptoms in this case might be explained by azotemia, congestive heart failure, anemia, superimposed infection or diabetes, all of which, however, were clinically more serious at times when she was not mentally disturbed. Brain involvement by an undetermined systemic disease is a possibility without supportive evidence.

Case 8. M. M. (M. G. H. 735279), a 35-year-old single woman, was admitted to the hospital on April 20, 1951, for treatment of postencephalitic, unilateral paralysis agitans, progressive since 1942. For several months before admission, she had received Panparnit, Artane and Thephorin, and although she was occasionally tense, these drugs had no adverse psychic effects. She was described as "immature," but there was no past history of overt psychiatric illness.

From April 24 through April 26, she received 75 mg. of cortisone by mouth twice a day. The other drugs were continued. On the evening of the 1st day of treatment she became depressed, felt "empty inside" and had a "sinking feeling" in her epigastrium. On the following day a severe depression, with illusions of voices and hallucinations of paranoid-depressive quality developed. She lacked insight into her hallucinosis but remained co-operative and actually attempted to conceal her apprehension over the experience. On April 30, she had a brief visual hallucination of a checkerboard pattern on the ceiling. The condition gradually cleared after April 29. The voices were last heard on May 2. At discharge on May 5, her mental state was normal.

This patient's remarkable vulnerability may have been due to a sensitization to cortisone by the underlying neurologic disease. It is also possible that the drugs given for the paralysis agitans acted synergistically with cortisone to induce a toxic psychosis. Although there is no supportive evidence for either speculation, Artane has been known to produce mental disturbance, with delusions and hallucinations, in such patients.

Case 9. E. M. (M. G. H. 692064), a 36-year-old single woman, was admitted for treatment of an exacerbation of disseminated lupus erythematosus, which had first been diagnosed 5 years previously. After a severe relapse at the age of 33, she became depressed, with hallucinations and delusions involving violence and snakes. She was admitted to a mental hospital, where she recovered in 2 months without treatment. A diagnosis of manic-depressive psychosis, depressed phase, was made. During the next 2 years, she was admitted to the hospital 4 times for treatment of the lupus but had no recurrence of mental symptoms.

The patient was close to her mother, perfectionistic and rigid. She had never been interested in men. She worked effectively as a teacher.

At the time of admission the lupus was severe, but no peculiarities of behavior were noted. She received 2200 mg. of cortisone in 10 days. She was noted to be depressed on the 3rd day of treatment. On the 10th day she was caught just before leaping from a window in a suicide attempt. She then showed depressive paranoid delusions. She smeared urine and dirt. She heard voices accusing her of sexual offenses. She was transferred to a mental hospital, where she gradually recovered over a period of 3 months and was discharged home.

Case 10. M. B. (M. G. H. 364433), a 56-year-old unemployed chemist was admitted to the hospital in October, 1951, for treatment of severe osteitis deformans, which had developed slowly during the previous 15 years. In 1935, after the death of his parents and a business failure, he had suffered a depressive illness, with seclusiveness, self-pity, insomnia and suicidal ideas, that required admission to a mental hospital. He was discharged improved after 3 months. He was readmitted to the mental hospital in 1937 in a state of "great excitement, very emotional and irrational." He was discharged after 1 year with a diagnosis of manic-depressive psychosis and under guardianship, which was later removed. He remained "eccentric." In 1949, at the time of an external carotid ligation carried out in an effort to slow the progress of his cranial hyperostosis, no note was made of an abnormal mental state.

Before therapy nonpsychiatric observers recalled him as being garrulous, argumentative and unco-operative. ACTH was started on November 3 and continued through November 15. The total dose was 1040 mg. He became increasingly restless and talkative. On November 15 he was intensely agitated and suspicious, and expressed many ideas of reference, influence and persecution centering in the ward situation. Later, fragmentation of speech and ritualistic gesturing developed. He became mute, struck poses and made unintelligible marks instead of writing letters. There was a period of catatonic behavior, followed by flights of ideas, rhyming, punning and overactivity. By November 27 he had become quieter but still had intermittent outbursts of manic and paranoid behavior. He was transferred to a mental hospital, where he continued to show the same variable behavior, but he gradually improved without specific treatment and was discharged on December 24.

Case 11. D. O. (M. G. H. 659364), a 36-year-old housewife, was first admitted to the hospital on April 25, 1949, with a history of progressive Cushing's disease of 2½ years' duration. Her illness had not been complicated by serious psychiatric symptoms. Subtotal adrenalectomy on the right was performed in May; the left adrenal gland was excised in March, 1951, with further subtotal resection of the right adrenal gland in April. She was maintained on DOCA and small amounts of cortisone because of moderate hypoadrenalism. From June 18 to June 23, she received 345 mg. of cortisone by mouth to prevent what was believed to be impending Addisonian crisis. On July 2 maintenance doses of cortisone at an average rate of 19.8 mg. daily were started. She was discharged on July 13 on a dosage of 25 mg. a day. However, it appears that by error she took 100 mg. a day for at least part of the subsequent 10-day period.

On July 21, the family reported that she had become acutely disturbed, expressing delusions of sexual assault and making many irrational telephone calls. She was readmitted to the hospital on July 23. She was found to be intensely agitated, suspicious, emotionally labile and talkative. She talked incoherently of "peeping Toms" and of being an "incognito FBI agent" engaged in counterespionage, "Code Number 659364" (actually, her hospital unit number). On subsequent days she was preoccupied, with delusional ideas of grandeur and persecution. There was marked anorexia, insomnia and restlessness. There were delusions of sexual assaults reinforced by visual and tactile (genital) hallucinations. However, she remained oriented concerning place and persons and was co-operative in medical care.

Gradually, her mental state improved, lucid intervals occurring more frequently. Recovery was complete by August 19.

An electroencephalographic tracing on August 6 was remarkable for scattered bursts of waves, 3 to 4 per second, occurring bilaterally. Subsequent tracings showed improvement. One taken on August 15 was within normal limits.

From July 26 to August 14 the patient received 25 mg. of testosterone propionate a day. There was no evidence that this drug modified the course of her recovery.

Case 12. F. G. (M. G. H. 669169), a 60-year-old man, was admitted to the hospital for balance studies on the metabolic ward. He had been well until 2½ years before admission, when he was found to have prostatic carcinoma with spinal metastases. Transurethral prostatectomy, bilateral orchidectomy and later a course of stilbestrol had brought temporary relief of pain. Three months before admission, he had undergone bilateral adrenalectomy in a further effort to retard the growth of the cancer. The pain was again relieved. He received replacement therapy postoperatively, and after discharge was maintained on implanted pellets of DOCA and daily doses of cortisone, which were started as 25 mg. and later reduced to 6.25 mg. a day. He had remained on this dose for over a month before entry.

There was no history of previous mental symptoms. He had led an active life and was well liked by friends and neighbors.

While on the ward, he began to complain of weakness and nausea. The cortisone was therefore increased to 31.25 and 25 mg. on 2 successive days. The eosinophil count fell from the range of 200-400 to 94. Coincidentally, he became agitated and confused. He experienced hallucinations of cats and balls of fire and developed the idea that a "fakir," in bright-colored clothing and selling little dolls, had raped his wife on the ward. He knew the current date but was completely wrong on dates of hospitalization. Neurologic examination was not remarkable. Cortisone was stopped immediately. During the next 7 days, he became quieter and less paranoid, and the hallucinations disappeared. Occasionally he was slightly confused, particularly at night.

After a lucid period of 6 days, he again became suddenly excited, believing he was being attacked by 2 Negroes and was to be killed. He had gained about 1 kg. in weight shortly before this relapse. This episode resembled the previous one. He slowly became quieter and lost his hallucinations and delusions. However, he remained uncertain of recent events and of the motivation of people around him.

Cortisone was started again in a dosage of 6.25 mg. a day. After 11 days of comparative quiet, he again became confused, excited and more paranoid, again saying that he had been awakened by a Negro, who was going to kill him. This episode occurred when the cortisone was increased to 12.5 mg. and subsided when the dose was returned to 6.25 mg. a day.

The patient was discharged, and the cortisone gradually increased to 25 mg. a day. He remained suspicous and became childish, — for example, he bought toy guns to frighten away attackers. However, there were no periods of excitement. By mistake, he gave himself 100 mg. a day for 11 days without known increase in the symptoms.

He was subsequently readmitted to the hospital for a pathologic fracture and died after 2 months. During this time, he received 60 mg. or cortisone a day. He was occasionally confused but did not become excited or deluded. At post-mortem examination, widespread metastases were found, including some in the meninges but none in the brain.

Case 13. A. E. (M. G. H. 270561), a 46-year-old man, was first seen in 1940. He complained of muscular weakness and was found to have cervicothoracic muscular wasting, testicular atrophy and deficiency of hair in the apocrine areas; x-ray examination of the skull revealed slight sellar erosion. There was increased spinal-fluid protein but no increase in pressure. Diagnoses of atypical myotonia dystrophica and probable pituitary tumor were considered. He was discharged but returned in 3 weeks for readmission. At this time a striking change in his mental state was noted. He seemed distracted and complained that his thinking was not clear. He complained of forgetting a thought before completing a sentence. On occasion, he staggered, did not talk sensibly and was depressed. Orientation and memory were normal. The character of these mental symptoms remains obscure.

He received x-ray therapy to his pituitary gland and returned to full activity. He was well for the next 10 years.

On October 10, 1951, he was readmitted to the hospital with a history of progressive bitemporal hemianopsia for 6 months, increasing weakness and episodic attacks described as "brown-out spells." During these attacks motor co-ordination was impaired, and he found it difficult to keep his thoughts in order.

It was decided that he should receive x-ray therapy, but in the event that rapid deterioration occured, emergency craniotomy could be carried out. The visual fields were examined each day, and he received ACTH because of the possibility of pituitary surgery. ACTH was started on October 27, and he received 775 mg. over the next 9 days.

On November 3 queer somatic illusions developed, which he described as follows: "I am all saturated with salt and water." He was oriented and rational. ACTH was stopped on the following day, but he became extremely agitated. Fever appeared on November 6. He had vivid hallucinatory images, many reflecting a disturbance of his body image. He believed that his pituitary gland was in the light above his head. Craniotomy was not considered feasible. He received testosterone propionate from November 8 to 13, without effect upon his mental state. He became increasingly febrile and unresponsive and died on November 16.

Post-mortem examination revealed a large chromophobe pituitary adenoma, with necrosis secondary to x-ray therapy, and lobar pneumonia. The tumor had pressed upward, deeply excavating the hypothalamic region.

This case exemplifies the difficulties that may be involved in the interpretation of mental disturbance arising on hormonal therapy since important factors contributing to it may have been the previous psychologic problems, the pituitary tumor, the effects of x-ray therapy, the toxic effects of lobar pneumonia and the ACTH.

Discussion

Cases 1, 2 and 3 represent relatively uncomplicated instances of hormonally induced psychosis, resembling the "major cases" of the previous report.[1] Cases 4 and 5 were emotionally unstable at the time treatment was started, and Case 6 was in the recovery phase of a previous nonhormonal, presumably "toxic" psychosis. Case 7 suffered a psychosis while on ACTH but in the presence of a number of other factors that might have contributed to the occurrence of mental disorder. Case 8 had known brain disease — that is, postencephalitic paralysis agitans. Cases 7 and 8 are remarkable for the relatively small amount of hormone given before untoward mental symptoms appeared. Cases 9 and 10 had a previous history of psychotic breakdown. Cases 11 and 12 had hypoadrenalism, as a result of adrenalectomy, whereas Case 13 suffered from hypopituitarism with secondary hypoadrenalism because of the compressive effects of a chromophobe adenoma of the pituitary gland. Additional factors complicating the interpretation of the mental symptoms of Cases 12 and 13 have been described.

As in the previous series, there is no statistically valid correlation between the total dose, duration of treatment or average dose on the one hand and the duration or severity of the resulting psychosis on the other. In general, there were more cases of prolonged ACTH treatment in lower dosage in the previous series than in the present one. However, in

several of the present cases, ACTH in large doses was given intravenously rather than intramuscularly. This fact complicates any direct comparison of doses. The duration and severity of the psychoses were not greater in patients exhibiting unusual sensitivity to hormonal therapy — that is, those (Cases 7, 8, 11 and 12) who broke down early after relatively small amounts of hormone. Case 8, for example, in whom hallucinations appeared after 300 mg. of cortisone, recovered within only six days.

Accordingly, the occurrence of these disorders does not appear to represent a matter of simple overdosage. It is also of interest that clinical signs of overdosage (moon facies, acne, hirsutism and so forth) and electrolyte evidence of hyperadrenalism did not correlate with the occurrence of psychiatric complications. This suggests that the mechanism involved in these disorders of cerebral function may be different from those involved in these other manifestations of overdosage. The same comments can be made regarding the abnormalities that are observed on the electroencephalogram during cortisone and ACTH therapy. Cases 1 and 11 demonstrated such abnormalities coincident with psychiatric symptoms. However, the previous experience as well as that of others[3, 4] has shown that such a concurrence is not invariably present.

There is no evidence from this series of cases that patients with emotional instability, inadequate social adjustment or in fact a history of previous psychotic episodes are liable to psychotic breakdown sooner or on lower dosage of hormone than those without these features of previous personality disorders. The low dosage involved in Cases 7 and 8 has already been mentioned. Considerable sensitivity to hormonal therapy was also shown in Cases 11, 12 and 13. The possible significance of hypoadrenalism in this regard will subsequently be discussed.

In a majority of these cases, frequent determinations of sodium, potassium, chloride and carbon dioxide were available before, during and after the psychotic episodes. No correlations were made between serum levels of these electrolytes and the mental state. Most of the patients received supplementary potassium chloride by mouth during hormonal therapy.

The symptomatology and clinical course in this series were similar to those characterized at length in our previous report. Again, many of the symptoms and mechanisms seen in the schizoaffective group of psychoses were evidenced. Disorientation and confusion occurred in Cases 5, 6 and 7, who were coincidentally quite ill from a medical standpoint, and terminally in the fatal Cases 12 and 13. It is doubtful if these events in the latter cases can be ascribed to hormonal treatment. In general, these classic features of "toxic psychoses" — that is, disorientation and confusion, — are not characteristic of psychoses associated with ACTH and cortisone.

The clinical course of these psychoses was again more remarkable for its variability and unpredictability than any other feature. The mental disturbance in Case 7, for example, occurred in three fairly discrete episodes, separated by intervals of relative lucidity. The first was a retarded depression without delusions or confusion, the second an acute confusional state without obvious depression, and the third an acute, severe delusional depression with marked negativism and mutism.

It is an interesting fact, as yet unexplainable, that patients may have tolerated previous courses of ACTH or cortisone without complications and yet become psychotic during a subsequent course of treatment with comparable or even smaller doses. This was true in Cases 2, 3, 4, 5 and 7. Case 2, for example, had three previous courses of ACTH and one of cortisone and then became psychotic on cortisone. Case 3 had tolerated well a course of ACTH but later became disturbed on cortisone.

The duration of the psychoses in the patients with a previous history of psychotic breakdown considerably exceeded the mean duration for the total series. This observation would be of interest if verified by a statistically significant series of cases. Another point of interest in these 2 patients is that the psychotic episode during hormonal therapy differed significantly from a symptomatic standpoint from the previous psychotic breakdowns. Answers to this general problem — that is, the relation of ACTH and cortisone psychoses to spontaneously occurring psychoses—must await further study of the effects of hormonal therapy on patients with a past history of psychosis.

The effects of cortisone and ACTH on patients with hypoadrenalism is of special interest in view of the use of these agents as replacement therapy. Cases 11 and 12 of this series suggest that patients with hypoadrenalism, in these cases secondary to surgical resection of the gland, are more sensitive, not only, as is well known, to the general metabolic effects of cortisone but also to the psychiatric complications. Case 11 tolerated fairly large doses of cortisone in the immediate postoperative period, presumably a period of stress with increased tissue needs and of impaired function of the adrenal remnant after the trauma of surgery. Later, during a phase of gradual recovery of endogenous adrenal output, she suffered a psychosis shortly after dosage was accidentally increased from 25 to 100 mg. a day. After recovery from this episode, she was maintained on 6.25 mg. of cortisone a day without further psychiatric complications.

Case 12, after several months of treatment with cortisone in doses of 6.25 to 12.5 mg. a day, became psychotic when the dose of cortisone was increased to 31.25 and 25.0 mg. on two successive days. Another

psychotic episode coincided with an increase in dosage from 6.25 to 12.5 mg. daily and subsided with return to the previous level. Paradoxically, however, during the terminal months of the disease, when he had become persistently childish, suspicious and at times confused, a considerable increase in dosage did not aggravate the already abnormal mental state.

Case 13 had hypopituitarism secondary to compression by a chromophobe adenoma of the pituitary gland. Severe deterioration of the mental state occurred after eight days of treatment with ACTH at an average dose of 86 mg. a day. However, as pointed out above, the presence of an intracranial neoplasm, an undetected lobar pneumonia and the fact that the disease had previously been associated with mental symptoms invalidate any definite conclusions about the sequence of events in this case.

On the basis of our experience to date, a number of points of importance to those using ACTH and cortisone are suggested. In the first place, absence of a history of psychotic breakdown or of defective emotional adjustment is no guarantee against the occurrence of a psychosis during hormone therapy. Secondly, tolerance of previous courses of ACTH or cortisone is similarly not valid assurance that psychotic breakdown will not occur during subsequent treatment with either of these agents. Thirdly, particular caution is indicated in replacement therapy for patients with primary or secondary hypoadrenalism. Fourthly, spontaneous recovery, except when interrupted by death of the patient from the underlying disease, occurred in all cases. Fifthly, a frequent pattern of recovery is by the occurrence of lucid intervals of increasing frequency and duration, punctuated by relapses into psychotic behavior — accordingly, patients should remain under careful observation for a reasonable period after apparent recovery in that temporary relapse is a likely possibility. Finally, each patient in whom a mental disturbance arises during hormonal treatment should be carefully studied for the presence of intracranial disease, metabolic disorders or other circumstances that may disturb cerebral function before cortisone or ACTH is definitely implicated as the responsible agent; this is of particular importance when cessation of therapy may seriously jeopardize the welfare of the patient.

Summary

A series of 13 cases of psychosis arising during therapy with ACTH or cortisone is presented. The clinical course and symptomatology of these episodes resembled that of other cases previously reported.

The cases included patients with a history of psychotic breakdown or defective emotional adjustment, with primary or secondary disease of the central nervous system and with underlying endocrinologic dysfunction. Evidence from the case material relevant to the possible relation of these circumstances to the occurrence of hormonal psychosis is discussed. Patients with hypoadrenalism appear to be both metabolically and psychiatrically sensitive to cortisone and require careful adjustment of dosage.

A number of points of practical value in the clinical management of patients suffering these psychiatric complications are discussed.

References

1. Clark, L. D., Bauer, W., and Cobb, S. Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. *New Eng. J. Med.* 246:205-216, 1952.
2. Quarton, G. C., Clark, L. D., Cobb, S., and Bauer, W. Unpublished data.
3. Lide, T., Carter, J. D., Lewis, B. I., and Surratt, C. Effects of ACTH and cortisone on mood and mentation. *Psychosom. Med.* 14:363-377, 1952.
4. Schieve, J. F., Scheinberg, P., and Wilson, W. P. Effect of adrenocorticotrophic hormone (ACTH) on cerebral blood flow and metabolism. *J. Clin. Investigation* 30:1527-1529, 1951.

ON DISREGARDING FINDINGS THAT CANNOT EXPLAIN THE SYNDROME*

WALTER C. ALVAREZ, M.D.†

CHICAGO, ILLINOIS

IN these days when so many physicians are looking to the laboratory worker, the roentgenologist and the specialist for most of their diagnoses, one of the most sorely needed courses in every medical school is one on the art of disregarding findings that turn up during many an examination but are not producing the symptoms and cannot possibly explain the whole syndrome presented by the patient.

That this instruction is badly needed today would be obvious to anyone who came and sat for a week alongside me at my desk. Often the condition reported by the patient's physician is present, but it is silent; it is harmless, and has no more to do with the patient's disability than the large wen on the back of his neck or the limp from an old attack of poliomyelitis.

AN UNRECOGNIZED STROKE

The other day I saw a fifty-five-year-old executive who had just been seen by an associate professor of medicine (I mention this fact simply to show that the mistakes I am worrying about are being made not only in the country but also in high places). The patient had a letter saying that at a university hospital he had had the usual series of tests and x-ray examinations, and that his trouble was a spastic colon.

Why was a diagnosis of spastic colon made? Simply because that was the only positive report that had come out of the diagnostic mill, much like the slip of paper that the taxi driver grinds out of his meter at the end of one's ride. What disturbed me about this affair was that the real diagnosis could have been made at a glance by any observant layman. As the man got out of the chair in my waiting room, it was obvious that something had hit his nervous system quite hard: he was slow and awkward, and when he walked toward me he took the short, uncertain steps of a person who has had a little stroke.

The minute he spoke, I saw that one side of his face was not as mobile as the other, and he had a tiny trickle of saliva coming out of one corner of his mouth. His clothes were not clean or properly pressed as an executive's should have been. As he answered my questions it was obvious that he was a bit slowed up mentally; I asked, and learned as I had expected that for months he had been unable to do any work. It was no longer possible for him to estimate contracts or even to dictate answers to his correspondence.

I asked his wife if the trouble had come suddenly, and she said, "Yes, on New Years' Eve." They were taking down the Christmas tree, when he collapsed and dropped to the floor. The family doctor, who thought the patient had had a heart attack, gave him some penicillin and took him to the hospital, where many electrocardiograms were made but nothing showed up. The doctor finally concluded that he had had a touch of influenza. Then the patient traveled to the great university center and had a thorough examination, which he and the professor believed would surely make the diagnosis.

From the medical report the man brought me it was obvious that the resident who took the history had not elicited any part of the essential story. He had put down only the patient's complaints about his insomnia and the discomforts in his abdomen. What was most remarkable was the obvious fact that no one had looked at the man as a human being; nobody had noticed that he was down and out, and nobody had noticed or suspected that something had hit his brain.

Why were these obvious signs missed? There could be only one explanation: the professor had expected to make the diagnosis only from the reports that came to his desk. He accepted these reports and looked no farther. He was practicing what I call decerebrate medicine.

SILENT GALLSTONES AND AN IDIOT CHILD

One day a woman came in with symptoms that indicated great fatigue and mental distress, with some insomnia, headache and backache. My assistant sent her for a thorough examination, and when the report came back that she had gallstones, in a functioning gall bladder, he was perfectly satisfied; he accepted cholecystitis as his diagnosis for her. I was not satisfied because, as I promptly showed my assistant, there was nothing in the woman's history that could be explained by her gallstones. She had no gas and she had never had colic. The stones were silent, as they are in half the cases.

More questioning quickly showed that what was really the matter with the woman was that she had an idiot child who for years, had kept her chained to her home, and as a result, her husband had been unfaithful to her. This distressed her greatly, and she was almost desperate because of the trap in which she was caught.

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 19, 1953.

†Editor-in-chief, *Modern Medicine*; emeritus professor of medicine, University of Minnesota Medical School.

Interestingly enough, this woman went back to her city, where, much against my advice, a local surgeon promptly removed her gall bladder. Evidently, from what he said, it could never occur to him that a finding like gallstones could have nothing to do with the case. All she got out of her operation was a distressing diarrhea.

On Gaining Sense Through the Years

As I look back on my medical youth, I am now appalled to think how, when recently out of college, I tried to ascribe all a woman's many neurotic symptoms to such silent and harmless things as a small ventral hernia, a torn cervix, a retroverted uterus, a ptosis of the stomach or colon, a mucous colitis, an achlorhydria, a sacralized fifth lumbar vertebra or a slight anemia.

Silent Amebiasis

Fortunately, I eventually learned how innocuous most of these conditions usually are. I learned this by never forgetting the patients who came in with something that at first looked serious but was later found to be producing no symptoms. For instance, one day a husky Mexican rancher, never sick a day in his life, asked me to put him through a thorough examination, just to please his wife. When in his stools were found enormous numbers of almost every type of intestinal parasite that one sees in the tropics, I quizzed him again and again but could get no history of his ever having had any indigestion, diarrhea, abdominal discomfort, poor health or anemia. In his case all the parasites were perfectly harmless.

Yet I have seen many physicians try to blame all a highly neurotic woman's troubles on a few amebic cysts that they had found with difficulty, and only after the study of half a dozen stools. To my way of thinking it was like trying to ascribe all her troubles to a couple of fleas that had been found on her when she came in.

I have seen many persons brought in with a diagnosis of amebiasis who actually had a far more serious diagnosis. One, the wife of a university professor, had a full-blown depression; another, referred to me by a distinguished professor of medicine, had an unrecognized exophthalmic goiter, another had a cancer of the rectum, and still another had a typical chronic ulcerative colitis.

Patients with Many Findings

To show how a physician must not clutch at diagnostic straws, I often tell the story of the stout, foreign-born, weepy and whiney woman who came to the Mayo Clinic to find out why she was so miserable. When she appeared for the final summing up, she was terribly distressed because, as she said, I had not found anything wrong with her. I answered that that was not my trouble; I had found enough things wrong, but no one of them had anything to do with her symptoms. For instance, she had a moderate hypertension, but, like most women with a Grade 1 hypertension, she had no obvious symptoms from it. It was not worth treating. She had some gallstones floating in a normally functioning gall bladder and, as usual, no symptoms. She had a few small kidney stones, but they were so well imbedded in the kidney substance that they were not producing any symptoms.

She had a basal metabolic rate of + 35 per cent, but since the removal of most of her thyroid gland by her home surgeon had not helped any, my colleagues in the thyroid division of the Clinic believed that the elevated rate was probably due to her nervousness or hypertension, and that she should not have any more of the gland removed. She had some myomas in her uterus but they were silent. She had a chronic urethritis, Grade 1, but it was of the type that gets worse if much treated. She had some varicose veins, but they were not causing trouble.

Why, then, was the woman suffering so much? Simply because her husband, having become fed up with her constant complaining, had gone off with a younger and merrier woman! That I did not know how to cure.

Patients with Serious Disease and No Symptoms

Whenever I see a person with gallstones and no symptoms, or severe amebiasis and no symptoms, I think that if I were teaching undergraduates in a medical school I would make a particular effort to show often in the amphitheater or in the wards patients who have striking findings, but no symptoms from them. My idea would be to prepare the students for the day when a patient will come in, as one did as I was writing this, and try to blame all his distress on some slight abnormality.

This man was feeling miserable, "thick in the head," tired and slightly uncertain of his balance, after passing a small tarry stool. His doctor thought he could blame the man's discomforts on an ulcer and an "anemia" with a hemoglobin reading of 85 per cent. I much doubted this, and looked for another explanation. Why? Largely because, years ago, I saw a merry, hard-working woman whose only complaint was that for months she had been bleeding badly from some hemorrhoids. With a hemoglobin reading of only 50 per cent, she said she felt wonderfully well and full of pep. My patient I now find has had two dizzy and confused spells in which he fell down, and these, I suspect, were due to the thrombosis of a couple of little blood vessels in the brain. Such a diagnosis could better explain his lack of a sense of good balance than a diagnosis of ulcer and anemia.

Often, when a medical associate tries to explain a woman's many nervous distresses on the basis

of some supposedly slight disturbance in some gland of internal secretion, I think of all the strong, uncomplaining symptomless women I have seen who had acromegaly, or an old myxedema, or a large rubbery goiter, diabetes, or castration early in life.

Such experiences always make me reluctant to blame serious symptoms on some so-called subclinical disease. It is conceivable and even probable that there are such diseases, but the physician who is constantly diagnosing them is likely soon to lose his scientific soul.

As I said, if I were teaching students I would show them people like one of my old patients who comes in occasionally to see me with a well compensated cirrhosis of the liver and still, after several years, a dye retention, Grade 3. He maintains that he has a cast-iron digestion and not a symptom in the world. I would show my students the many persons I see with silent symptomless bundle-branch blocks discovered accidentally. I would show them persons who, for thirty years, have been known to have a diaphragmatic hernia—without any symptoms to talk about. I would show women in the menopause without a symptom, or women with a sacralized fifth lumbar vertebra and no backache, or persons with tremendous hyperostoses on certain vertebras, and no symptoms.

The Final Test of a Clinician

I often think that if I were asked quickly to examine a group of men applying for the Diploma of the National Board of Internal Medicine I would test them on a patient suffering from a severe neurosis, bad migraine or mild psychosis, or the results of a little stroke, but with silent stones in the gall bladder, an old, long healed "duodenal ulcer," a movable but silent and harmless right kidney, a harmless diverticulum of the duodenum, a silent diaphragmatic hernia, a colon covered with silent and harmless diverticula, some harmless cervical ribs, a silent myoma of the uterus, a large but harmless retrocecal appendix, a loud but harmless congenital heart murmur or a symptomless bundle-branch block.

The applicants who had enough clinical sense and wisdom not to grasp quickly and happily and confidently at the diagnostic straw offered them would be passed; the rest would be deferred. They, obviously, could not yet have attained unto clinical wisdom. They would still be ordinary push-button diagnosticians, men like the head of a small clinic, who, on introducing me to his laboratory assistant, said; "Here's the woman who makes my diagnoses." How fearful I was that he was telling the truth!

Summary

Obviously, today, many diagnoses of neuroses, minor psychoses, little strokes, migraine and so forth, can be made only by the physician who will take a good history and observe his patient closely.

The doctor who takes a poor history, does not look at the patient, and accepts unthinkingly the diagnosis that is handed him by the laboratory assistant or the roentgenologist is daily making terrible blunders. Many of the things he diagnoses are silent and symptomless and have nothing to do with the patient's illness.

The saddest feature of all this is that this "push-button" type of decerebrate medicine is being practiced, not so much, perhaps, in the villages, as in the university centers.

700 North Michigan Avenue

MEDICAL PROGRESS

THE APPLICATION OF TISSUE-CULTURE METHODS TO THE STUDY OF POLIOMYELITIS*

Thomas H. Weller, M. D.†

BOSTON

PROGRESS toward the control or understanding of the epidemiology of a specific infectious disease has often been associated with the development of a new procedure for the isolation or cultivation of the etiologic agent. An example of the effect of such a technologic advance is apparent in the field of research on poliomyelitis. In 1949[1, 2] it was demonstrated that the poliomyelitis viruses could be propagated in tissue cultures composed of nonnervous human tissues. Since then, the application of tissue-culture methods has resulted in the development of simple and economical procedures for the isolation of the poliomyelitis viruses and for the serologic diagnosis of the infections that they produce. These procedures, now utilized in more than 20 research centers in the United States, have not yet come to the attention of the medical profession in general. However, it may be predicted on the basis of work in progress that the laboratory diagnosis of infection with the poliomyelitis viruses by the use of simplified tissue-culture technics will

*From the Research Division of Infectious Diseases, Children's Medical Center, and the Department of Tropical Public Health, Harvard School of Public Health.

†Associate professor of tropical public health, Harvard School of Public Health; assistant director, Research Division of Infectious Diseases, and associate physician, Children's Medical Center.

Aided by a grant from the National Foundation for Infantile Paralysis.

become an accepted function of the public-health or large hospital laboratory in the future.

This report first describes in a general manner tissue-culture methods, with particular attention to those employed in poliomyelitis research. It is not my intent to review the subject of tissue culture and its uses in the study of viruses. Those desiring information on the methodology of tissue cultures are referred to books by Parker and Morgan[3] and Cameron.[4] Robbins and Enders[5] recently reviewed studies on animal viruses utilizing the technic of tissue culture. It is to be noted that the present-day yellow-fever vaccine, which is composed of living virus modified by tissue-culture passage,[6] remains the classic example of the practical application of tissue-culture methods in the field of virology.

Tissue-Culture Methods

The viruses, without exception, multiply only in the presence of living cells. Investigators have tended to rely on the laboratory animal or, more recently, the embryonated hen's egg as the medium for isolation and propagation of these agents. Tissue culture technics were developed by those interested primarily in morphology or experimental physiology. Although the Maitlands'[7] demonstration that vaccinia virus could be propagated in a simple tissue-culture system stimulated studies on the cultivation of a variety of viruses, virologists generally have been reluctant to explore the method. Recent advances should mitigate this reluctance. At present the technics have been modified to the point that, given proper preparation of glassware, satisfactory tissue-culture work can be performed in most laboratories equipped to carry out routine bacteriologic procedures. The incorporation of antibiotics in tissue-culture mediums has, for practical purposes, eliminated bacterial contamination. Standardized constituents of such mediums may now be obtained commercially. Tissues, singularly suitable for the investigation of the virus infections of man, are readily available as the by-products of certain common surgical procedures.[2, 8-11]

There are two general types of tissue cultures, and both technics have been employed in studies on the poliomyelitis viruses. For simplicity these may be termed the "suspended-cell" and the "fixed-cell" procedures. In the former, finely minced fragments of tissue are introduced into small flasks and float or settle in the shallow layer of nutrient medium. In the latter, the tissue fragments are planted on a substrate, most often a thin layer of clotted plasma, or else grow directly on the wall of the container.

The simplest form of fixed-cell culture is the plasma hanging-drop technic, which is useful for short-term morphologic investigations. The roller-tube procedure, first employed in studies of virus cultivation by Gey and Bang,[12] represents a modification of this principle and has been extensively employed in the cultivation of the poliomyelitis viruses. Tissue fragments are distributed on the wall of test tubes or various types of bottles,[13, 14] usually in a thin layer of plasma; the plasma is then clotted by the addition of a few drops of embryonic extract. A small amount of nutrient medium is added, the tubes are stoppered, and the cultures are incubated in an almost horizontal position in a

FIGURE 1. *Roller-Tube Tissue-Culture Apparatus Employed in Poliomyelitis Research.*
One drum contains tubes, and the other roller bottles.

drum, which rotates slowly (Fig. 1). The process of rotation alternately covers the growing tissue with nutrient and exposes it to the air in the culture. Excellent growth is achieved, and by periodic replacement of the nutrient fluid, active cellular multiplication can be maintained for long periods. One difficulty previously encountered in cultures kept for many days — namely, the gradual lysis of the supporting plasma clot by the growing tissue — has been overcome by the incorporation in the medium of soybean trypsin inhibitor[11] as originally described by Fischer[15] and Morgan and Parker.[16]

The nutrient medium has generally consisted of an isotonic buffered saline solution, such as Tyrode's[3] or Hanks',[17] together with varying amounts of serum and embryonic extract. The last

two components provide factors, not as yet defined, that are essential for the continued growth and multiplication of cells. The addition of small amounts of a nontoxic indicator such as phenol red permits visual appraisal of the metabolic activity of the growing tissue, as evidenced by the progressive fall of pH of the medium.

Modifications of this basic nutrient medium are introduced to achieve various objectives. Recently, Enders[18] described the growth-promoting properties of bovine amniotic fluid, and this substance supplemented with small amounts of horse serum and beef embryonic extract is now routinely employed by him when the primary objective is to achieve excellent tissue growth. When it is desired to obtain virus for immunologic studies an attempt is made to reduce the concentration of extraneous protein in the medium. The protein-free ultrafiltrates of serum introduced by Simms and Sanders[19] are then especially useful, as are various synthetic mediums. Although for certain purposes the use of such protein-free mediums is desirable, in general the tissue growth thus achieved is inferior to that obtained with the standard mediums. Therefore, difficulties may be encountered if the simplified mediums are employed routinely.

The Poliomyelitis Viruses

Before the contributions of the tissue-culture method to the problems of poliomyelitis are considered in detail, it may be helpful to review pertinent facts concerning the agents responsible for this disease. In 1909 Landsteiner and Popper[20] observed that a febrile illness with flaccid paralysis was produced in monkeys after inoculation with material obtained from a patient with poliomyelitis. Until recently, inoculation of monkeys has remained the only means of isolating these viruses and the production in the monkey of the characteristic myelitis with anterior-horn-cell degeneration has been the criterion for the identification of this group of agents. The dependence of the poliomyelitis research laboratory on the availability of monkeys has limited the number of research centers. As Paul[21] pointed out in outlining the procedures employed in such a center, little diagnostic assistance could be given the clinician dealing with a suspected case of poliomyelitis. No practical serologic tests were available, and virus isolation studies were usually not feasible in the great majority of cases. Investigations were, of necessity, fundamental and concentrated on elucidating the pathogenesis, immunology and epidemiology of poliomyelitis. Present knowledge of this infection in the main represents the summation of data obtained as the result of an immense amount of difficult, expensive and protracted experimental work on the monkey. This statement needs partial qualification, for, in 1939, Armstrong[22] demonstrated that one strain of virus, now recognized as the prototype of the Lansing group, was capable of infecting rodents if inoculated by the intracerebral route. Investigation of certain aspects of the poliomyelitis problem was thereby expedited. For example, assay in mice of the neutralizing antibody content of human serum specimens collected in various countries has demonstrated that the Lansing type of virus (Type II) is worldwide in its distribution and indicates that poliomyelitis is not primarily a disease of temperate climates.[23]

Certain concepts regarding the poliomyelitis viruses here deserve mention. The first is the recognition that at least three antigenic types exist. Burnet and Macnamara,[24] in 1931, reported evidence for the existence of more than one immunologic type of virus. Other workers presented supporting data, but until 1948 no systematic attempt was made to establish the number of types of virus. In that year the National Foundation for Infantile Paralysis organized the Committee on Typing, under whose direction a co-operative project was undertaken by investigators at four universities. With standardized technics and thousands of monkeys, 100 different strains of poliomyelitis virus were classified. This co-operative study, published in 1951,[25] resulted in the grouping of these strains as follows: Type I (Brunhilde-like), 85 strains; Type II (Lansing-like), 12 strains; and Type III (Leon-like), 3 strains. The implications of these findings in the epidemiology of poliomyelitis and in the problem of the preparation of immunizing materials are obvious.

Ideas concerning the pathogenesis of poliomyelitis have undergone considerable change, but as yet this phenomenon is incompletely understood. The concept of poliomyelitis as a strictly neural disease has largely been supplanted by the view that it is primarily a disease of the gastrointestinal tract. This theory provides an explanation for the fecal excretion of large amounts of virus by patients with either nonparalytic or paralytic poliomyelitis. It has usually been assumed that spread of the virus from the gastrointestinal tract to the central nervous system occurs along the regional nerves. Recently, a transient viremia has been demonstrated in chimpanzees and cynomolgus monkeys[26, 27] infected by the oral route. This observation, as well as the recognition that specific antibodies are usually present by the time paralysis develops, led Bodian[27] to postulate a vascular phase of virus multiplication and to suggest that virus alternately may reach the central nervous system via the blood stream. The findings, described below, that the poliomyelitis viruses can be propagated in vitro in a variety of non-nervous tissues may be further evidence that the poliomyelitis viruses are not strictly neurotropic in vivo. However, although data continue to accumulate suggesting that the poliomyelitis viruses do indeed grow in the body in non-nervous tissues,

it must not be assumed that the results of the studies in vitro necessarily indicate that a similar process occurs in vivo.

In Vitro Cultivation of the Poliomyelitis Viruses

Development of Technics

In 1936 Sabin and Olitsky[28] described the propagation of poliomyelitis virus for six passages in cultures of human embryonic brain tissue but were unable to cultivate this agent in other human tissues. Four years later Burnet and Jackson,[29] in a single experiment, obtained suggestive evidence of viral multiplication in cultures of human pharyngeal and embryonic intestinal tissue. The subsequent demonstration of the cultivability of the poliomyelitis viruses in non-nervous tissues involved an element of chance. In 1948 it was observed that a slight modification of the suspended cell-culture technic, which involved frequent changes of the nutrient fluid and infrequent subculturing, permitted demonstration of the in vitro multiplication of mumps virus,[30] an agent that grows relatively slowly. This technic was next applied in attempts to isolate the etiologic agent of chickenpox,[31] and for this project suspended cell cultures containing human embryonic skin and muscle tissue were prepared. The availability of these cultures, as well as the accumulating indications that poliomyelitis virus might not be strictly neurotropic, led to their inoculation with the Lansing strain of poliomyelitis virus. After the demonstration that the Lansing virus multiplied in suspended cell cultures of embryonic skin and muscle tissue,[1] experiments were initiated with human embryonic intestinal and brain tissues. Subsequently, it became apparent that, in this culture system, the poliomyelitis viruses behave as mumps virus does, in that, after the introduction of a small inoculum, detectable level of virus is achieved slowly. It was also reported in 1949 that the Brunhilde strain could likewise be propagated, and that mature as well as embryonic tissues supported growth.[2] In 1950, the first confirmatory reports from other laboratories on the cultivability of the poliomyelitis viruses in non-nervous human tissues appeared.[8, 32]

Huang,[33] working with the western strain of equine-encephalomyelitis virus in cultures of chick tissues, observed that this virus destroyed cells in which it multiplied. The destructive effect was not apparent after the inoculation of cultures with virus neutralized by specific antiserum. Therefore, Huang was able to perform both titrations of virus content and neutralization tests in vitro employing the presence of specific morphologic changes as the indicator of viral activity.

The demonstration that the poliomyelitis viruses likewise exert a destructive action on cells when cultivated in vitro,[1, 34] termed the "cytopathogenic"[34] effect of the virus, has had immediate practical applications. Early in these studies it was noted that the metabolic activity of tissues infected with poliomyelitis virus was impaired. A difference between infected and control suspended cell cultures became apparent after two or more weeks of cultivation and was manifested by a failure of the pH of the medium to fall as rapidly as that of the controls. Histologic examination of tissues removed from infected cultures after prolonged cultivation showed degenerative changes not present in control materials. When fragments of tissue were removed from uninoculated suspended cell cultures and transplanted to plasma hanging drops, migration or growth of cells occurred. Fragments from cultures previously inoculated with the virus either exhibited no migration of cells or, if this occurred, quick degeneration of the cells. These procedures, although permitting demonstration of the cytopathogenic activity of poliomyelitis viruses, were long drawn out and tedious. It seemed, therefore, that the injurious effect of virus might be more easily and rapidly demonstrated in roller-tube cultures containing actively growing cells in thin layers. Roller cultures of human embryonic skin-muscle tissue were prepared in a manner similar to that previously employed in the study of vaccinia virus.[35] After growth had become established, the inoculation of poliomyelitis virus resulted in extensive cellular degeneration within a few days.[34] These changes were readily apparent when the tubes were observed under low magnification (Fig. 2). Furthermore, they were inhibited by type-specific antiserum; for example, the cytopathogenic effect of Lansing virus was neutralized by Lansing antiserum, but not by serums containing antibodies against the Brunhilde or Leon type of poliomyelitis virus. Thus, the specific cytopathogenic effect of the poliomyelitis viruses provided a simple indicator of viral activity. It appeared that under properly controlled conditions, for the isolation, titration or typing of these viruses, one tissue culture, in effect, could therefore replace one monkey.

In 1951 the tissue-culture method was successfully employed for the direct isolation and serologic identification of poliomyelitis virus from materials obtained from patients with nonparalytic and paralytic poliomyelitis.[36] Twelve strains were isolated from feces, and 1 from the spinal cord in a fatal case; of the 13 strains, 10 were classified by in vitro technics as Leon-like and 3 as Brunhilde-like. In these studies both suspended-cell and roller cultures were employed. However, the rapidity with which the cytopathogenic effect becomes apparent in roller tubes and the ease with which it may be observed has led to the use of the fixed-cell type of culture[11, 37, 38] for the isolation and identification of these agents. It has been found that human myometrium and foreskin, both readily available, grow well in roller

tubes, and these tissues are now employed routinely in the laboratories at the Children's Hospital. For certain purposes, the roller method has been simplified by others and slanted tubes that are not rolled have been used.[39, 40] Decreased utilization of glucose by infected tissues has been reported as yet another manifestation of the cytopathogenic action of the poliomyelitis viruses.[41]

The demonstration that certain monkey tissues[9, 42] support the growth of the poliomyelitis viruses in vitro was an important development. The availability of monkey tissues in the established poliomyelitis research center has led several groups to the extensive use of monkey testicular or kidney tissues.[43-45] The observation that tissues obtained from immune as well as normal monkeys support virus growth[46] was of both practical and theoretical interest.

It is to be expected that a progressive simplification and standardization of tissue-culture methods will occur as the technics are further adapted to large-scale use. Recently Scherer, Syverton, and Gey[47] reported the propagation of poliomyelitis viruses in cultures prepared with a strain of human malignant epithelial cells maintained for two years in the laboratory; this work points to a readily available supply of standardized human tissue. Simplification of mediums has been directed primarily to elimination of protein-containing materials. Melnick and Riordan[40] have employed a hydrolysate of lactalbumin. The synthetic tissue-culture medium developed by Morgan, Morton and Parker[48] was first utilized in studies on poliomyelitis by the Toronto group[14, 41, 49] and has now been adopted in several laboratories.

An important technical development was the demonstration by Svedmyr, Enders and Holloway[13,50] that satisfactory complement-fixing antigens for each of the three antigenic types of poliomyelitis could be prepared from the fluids harvested from infected cultures. Such fluids, concentrated by the filtration technic of Seibert,[51] were used in the drop complement-fixation procedure of Fulton and Dumbell.[52] Recently, certain strains of virus that produce high titers in roller cultures (tissue culture infectivity titer of $>10^{-6}$) have been propagated; with these strains, the infected culture fluid serves as a complement-fixing antigen without concentration.[53]

A B

FIGURE 2. *Preparations from Roller-Tube Cultures of Human Embryonic Skin-Muscle Tissue, Seven Days after Cultures were Initiated* (A) *and Three Days after Inoculation* (B) *with the Brunhilde Strain of Poliomyelitis Virus (Hematoxylin and Eosin Stain).*
Few cells remain in the infected culture (B), *the majority having been destroyed by the cytopathogenic action of the virus.*

Application of Technics

Study of the behavior of the poliomyelitis viruses in vitro. It is now apparent that the poliomyelitis viruses may be cultivated in vitro in a wide variety of non-nervous human tissues, both embryonic and mature, normal and malignant. Thus evidence of multiplication in cultures prepared with the following tissues was obtained[10, 11]: skin muscle, intestine, foreskin, testicle, spleen, heart, adrenal gland, uterus, thyroid gland, an embryoma and a neuroblastoma. Evidence of multiplication in tonsillar tissue[54] has also been educed. Illustrative of the experience with suspended cell cultures are the results

presented in Figure 3, summarizing the findings obtained with 9 different types of tissue derived from a single human embryo. Similarly, a variety of monkey tissues, including testicle, kidney,[10, 11, 44, 45, 55] muscle,[44, 48] lung[55] and intestine[55] will support multiplication in vitro. The results obtained with the tissues listed are not dependent upon the inclusion in these tissues of neural elements. The cytopathogenic effect of inoculation of tissue cultures with the poliomyelitis viruses appears to be the reflection of specific injury by these agents. Specific cytopathogenicity has been manifest in a variety of types of cells; indeed, with the exception of cartilage, no clearly resistant cell type has been encountered in these studies,[56] indicating that multi-

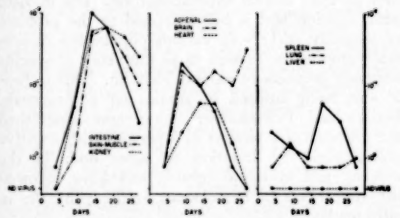


FIGURE 3. *Multiplication of the Lansing Strain in Suspended Cell Cultures of 9 Different Tissues Derived from a Single Human Embryo. (Reproduced from Weller et al.," with the Permission of the Publishers.)*

Mouse infectivity titers (LD_{50} dilution) of pools of fluids removed from the cultures at four-day intervals are demonstrated.

plication occurs in vitro in cells of diverse origins. Further evidence for this fact has been presented by Scherer and Syverton[57] who have cultivated poliomyelitis virus in morphologically pure cultures of monkey fibroblasts, and of human epithelial cells[47] derived from carcinoma of the cervix.

Various investigators have studied the pattern of multiplication of the poliomyelitis viruses in culture.[10, 11, 44, 49, 58, 59] After the introduction of a small inoculum there is a lag period before virus is detected in the fluid phase, the duration of which is probably influenced by the culture technic employed, the strain of virus and the type of tissue, as well as by the amount of virus inoculated. The lag phase is followed by a period of rapid release of virus into the fluid. Thereafter, virus is released at a reduced rate, which appears to be determined by the number of cells that have escaped infection and the condition of the culture per se. Scherer and Syverton[59] have presented convincing evidence that multiplication occurs in discrete cycles.

Brown, Ackermann and Schieble[58] first employed the culture method for studies on the biosynthesis of poliomyelitis virus. They presented evidence that l-methionine was essential for virus growth, multiplication being inhibited in the presence of the structural analogue, dl-ethionine. Investigations on additional antimetabolites are being continued by Brown[60, 61] and in other laboratories.

Various strains of virus have been observed to differ under in vitro conditions both in cytopathogenicity and in the infective titer attained. A low order of cytopathogenicity for monkey tissues has been noted in certain rodent-adapted strains,[60, 62, 63] particularly the Lansing strain. It has been established that the apparent infectivity of these viruses for animals may be altered on prolonged propagation in tissue culture. During the serial propagation of Lansing virus for periods up to three hundred and thirty-one days in human skin-muscle tissues, a marked decrease in the infectivity titer for the mouse was observed,[10] although virus production as assayed by the in vitro technic remained at a high level throughout. A similar reduction in mouse pathogenicity has been noted on cultivation of the Lansing strain in monkey tissue.[44] Serial cultivation of the Brunhilde strain in human embryonic skin-muscle tissue also resulted in a decrease in virulence of the virus for monkeys,[10, 64] although, again, no alteration of the capacity of the virus to multiply in vitro occurred. Thus, a majority of monkeys receiving an intracerebral inoculum of the passage virus containing 100,000 to 1,000,000 tissue-culture infective doses showed no paralysis. It is to be noted that the recognition of the decrease in animal pathogenicity observed on prolonged cultivation in this experiment was dependent on the availability of an alternative method of viral assay — namely, titration in vitro. Observations of this type are primarily of interest in demonstrating that the tissue-culture method may be applied to problems of developing and selecting mutants of altered pathogenicity. To date, the poliomyelitis viruses have been cultivated only in tissues of human or monkey origin. It is an interesting paradox that the Lansing group of agents that multiply in mouse tissues in vivo apparently fail to do so in vitro. On theoretical grounds, in attempts to develop a mutant suitable for use as a live immunizing agent, it would be desirable to employ tissues biologically unlike those of man. Attempts at propagation of the poliomyelitis viruses in cultures of chick tissues have been unsuccessful. In this connection the recently reported propagation of the MEF1 strain of poliomyelitis virus in the embryonated hen's egg[65, 66] has great potential significance.

Evidence of interference between the antigenic types of poliomyelitis virus in tissue culture has now been presented.[67] This observation represents another application of the culture method to the study of poliomyelitis virus and host cell relations.

Problems of diagnosis, pathogenesis and epidemiology of poliomyelitis. The diagnosis of a viral in-

fection is usually established by the demonstration of a characteristic pathologic change induced by the agent, by the isolation of the agent or by the demonstration of a rising titer of specific antibodies in paired blood specimens obtained from the patient. Tissue cultures are now employed in special laboratories for the isolation and identification of the poliomyelitis viruses and for the assay of specific antibodies, both for diagnostic purposes and in studies on the distribution of infection in population groups.

Poliomyelitis virus may be isolated from feces if cultures are inoculated with a portion of the supernatant of centrifuged fecal suspensions to which antibiotics have been added, and the cultures

TABLE 1. *Type Distribution of Poliomyelitis Viruses Isolated by the Tissue-Culture Method from Patients at the Children's Medical Center, Boston.**

YEAR	NO. OF VIRUSES TYPED	NO. OF VIRUSES BY TYPE		
		I (BRUNHILDE)	II (LANSING)	III (LEON)
1949	9	9	0	0
1950	22	3	0	19
1951	2	1	0	1
1952	53	38	8	7
Totals	86	51	8	27

*Combined data of Robbins et al.[36] and Kibrick and Enders.[70]

then observed for the appearance of cytopathogenic activity. It is necessary to demonstrate that the observed degenerative changes are specific by performance of in vitro neutralization tests. In brief, one performs these tests by inoculating new cultures with mixtures of the appropriate antiserums and fluids from the original cultures and again recording the presence or absence of cytopathogenicity. This procedure specifically identifies any poliomyelitis virus present. Typing of the virus thus isolated is an essential step, since fecal specimens may contain either nonspecific cytotoxic substances or, of more import, other viruses, such as certain members of the Coxsackie group, which may be cytopathogenic.[36-38, 68, 69] Kibrick and Enders[70] have continued earlier studies[36] on the isolation of poliomyelitis virus from fecal specimens obtained from patients admitted to the Children's Hospital in Boston with a diagnosis of paralytic or nonparalytic poliomyelitis. Some of the findings to date are summarized in Table 1; these demonstrate that all three types have been encountered. It is of interest that in this study, poliomyelitis virus has been isolated from 95 per cent of a group of 39 patients with paralysis and in only 64 per cent of those in a group of cases diagnosed clinically as nonparalytic poliomyelitis. Other workers are utilizing tissue culture in a similar manner: Riordan et al.[37] reported 21 isolations, Youngner and his co-workers[38] described 37 isolations, and Syverton and Scherer[71] recently noted the recovery and typing of 40 strains.

The development of antibodies during the course of an infection with the poliomyelitis viruses may be demonstrated by neutralization in vitro or by complement fixation employing tissue-culture virus as antigen. Additional work is necessary before the limitations of these procedures are defined and their practical diagnostic value established. In the light of present limited experience, it appears that infection is usually associated with the development of neutralizing antibody that is type specific, whereas the complement-fixation reaction demonstrates the appearance of antibodies that may be both type and group specific.[12, 68, 72] These observations are in general accord with those of previous workers derived from animal experimentation. The in vitro neutralization test is being applied to the problem of antibody surveys in various populations in several laboratories, as well as to the assay of specific antibody in pools of gamma globulin. This technic is also being utilized in studies on pathogenesis. Bodian and Paffenbarger[73] have now established the presence of a viremia in 3 persons with abortive poliomyelitis by isolation of virus both in the monkey and in tissue culture, and have followed the appearance of homologous antibody by the in vitro method.

To expedite the application of the culture technic to routine diagnostic problems studies are in progress that are designed to develop a simplified tissue-culture system that would be available commercially. It is possible that the hospital diagnostic laboratory will, in the future, be able to order cultures from a central supply source, and receive such cultures in a form ready to inoculate. Illustrative of effort in this direction is the observation of Syverton and Scherer[71] that cultures prepared with the "Hela" strain of human epithelial cells will withstand shipment by train or plane for long distances.

Problem of immunization. Ideally, the immunizing material of choice would be composed of live agents, devoid of pathogenicity, but retaining antigenicity. As noted above, experimental studies with tissue cultures in various laboratories are being directed toward the development of such attenuated viruses. The problem is manifestly difficult, for not one but at least three modified poliomyelitis viruses must be combined in a polyvalent vaccine. Attention has therefore been directed also to the potentialities of inactivated tissue-culture virus as immunizing material. Virus cultured in non-nervous tissue is obtainable in a concentration equal to or exceeding that present in infected monkey nervous tissue. Since it is devoid of the sensitizing components present in monkey tissue, such a cultured virus when injected does not present the problem of possible demyelinating encephalitis. In 1950, Milzer and his associates[52] noted that the intraperitoneal

injection of tissue-culture virus in mice conferred a degree of protection to subsequent intracerebral inoculation. In 1951 it was reported[74] that partial protection followed intramuscular inoculation of mice. In the following year Salk and his collaborators[75] made the significant observation that tissue-culture virus inoculated intramuscularly in monkeys was antigenic and that the incorporation of a mineral-oil adjuvant with the virus enhanced the antibody response. Furthermore, culture virus treated with formalin in minimal concentrations sufficient to destroy infectious activity was found to be antigenic. The antigenicity in monkeys of virus-adjuvant mixtures was also described by Wood et al.[14] Salk and his co-workers, in an extension of their studies, have now investigated the antibody response in children after the injection of inactivated virus produced in cultures of monkey testicular or kidney tissue. In a preliminary account of work in progress,[48] they report that inoculation of combined vaccine prepared with oil adjuvants and containing the three types of formalin-inactivated virus is followed by the appearance of antibodies against the three agents. The immunologic response approximates that produced by the pathologic process itself. Although they stress the preliminary nature of these findings, it is obvious that their observations constitute an important advance. It is to be noted that in this study the culture technic made possible the production of the immunizing material and was employed in the assay of its effectiveness.

Detection of previously unrecognized viruses. The application of tissue-culture methods to the problem of virus isolation from patients with a clinical diagnosis of poliomyelitis has resulted in the recovery from feces of cytopathogenic viruses that are not pathogenic for the monkey. In the original study of Robbins et al.[26] 2 such viruses were encountered. One remains unidentified and is probably a new entity; the other is a member of the Coxsackie group, which is cytopathogenic for a variety of human tissues[68] and has been classified by the Yale group as a new antigenic type (Boston).[76] Subsequently, 8 additional agents have been isolated[77] that are not typable poliomyelitis viruses. These viruses are of especial interest because they were all isolated from patients with nonparalytic poliomyelitis seen during 1951 at the Children's Hospital. At least 4 have been shown not to belong to the Coxsackie group. While their interrelations are being studied, the findings to date suggest that during 1951 infection with a hitherto unrecognized group of intestinal viruses was prevalent in Boston. Melnick and his associates[69] similarly isolated from human feces 10 agents that are cytopathogenic and are not neutralized by poliomyelitis-immune serums; 3 of these appear to be members of the Coxsackie group, but 7 still under investigation, appear to be unknown entities. These findings suggest that the application of tissue-culture technics will result in the detection of a number of previously unrecognized intestinal viruses, much as the introduction of the technic of isolation by inoculation of the suckling mouse has resulted in the recognition of the variety of viruses now loosely classified as the "Coxsackie group."

In 1949, Sabin and Steigman[78] reported the isolation of "poliomyelitis" virus of low virulence for the monkey from the stools of 4 patients with "summer grippe." One of these viruses, which in the monkey produced lesions confined to the olfactory portal, has now been studied in tissue culture by Steigman and Kokko.[79] It manifests a cytopathogenic effect but appears immunologically unrelated to the 3 recognized types of poliomyelitis virus. Its relation to those isolated in Boston and New Haven remains to be determined. The majority, if not all, of these new agents have been isolated from cases of so-called "nonparalytic poliomyelitis"; they may prove to be distinct from the true poliomyelitis viruses. However, it is to be recalled that until recently the poliomyelitis viruses were isolated in the monkey and are defined in terms of the pathologic changes observed in that animal.[80] It is possible that the use of tissue-culture isolation methods will reveal the existence of a fourth group of true poliomyelitis viruses, capable of producing paralysis in man and possessing little or no pathogenicity for the monkey. In the search for such a hypothetical poliomyelitis virus, as well as in other studies designed to isolate previously unrecognized etiologic agents from human infections, it appears desirable to use a human tissue-culture system.

Discussion

It is already apparent that the technical procedures reviewed above are applicable to the study of entities other than poliomyelitis. For example, the efforts to isolate the etiologic agent of varicella that originally led to the use of cultures prepared with human tissues have been continued, the improved technics developed during the studies on poliomyelitis being employed. Recently, cytopathogenic agents that produce intranuclear inclusions in vitro have been isolated from 6 different specimens of varicella vesicle fluid and passed serially in tissue culture; 2 agents having similar characteristics have likewise been obtained from patients with herpes zoster.[81] Another example of the application of these methods is found in the recent isolation in cultures of 7 cytopathogenic agents from patients observed during the epidemic of an exanthem of unknown etiology that occurred in the Boston area in the late summer of 1951.[82] Although, as previously emphasized, the conditions and phenomena observed in vitro are different from those obtained in vivo, it is obvious that the human tissue-culture system provides an alternative in certain cases at least

to the utilization of human volunteers in the study of the infectious entities of man that possess a high degree of host specificity.

References

1. Enders, J. F., Weller, T. H., and Robbins, F. C. Cultivation of Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. *Science* **109**:85-87, 1949.
2. Weller, T. H., Robbins, F. C., and Enders, J. F. Cultivation of poliomyelitis virus in cultures of human foreskin and embryonic tissues. *Proc. Soc. Exper. Biol. & Med.* **72**:153-155, 1949.
3. Parker, R. C., and Morgan, J. F. *Methods of Tissue Culture*. Second edition. 294 pp. New York: Hoeber, 1950.
4. Cameron, G. *Tissue Culture Technique*. 191 pp. New York: Academic Press, Incorporated, 1950.
5. Robbins, F. C., and Enders, J. F. Tissue culture techniques in study of animal viruses. *Am. J. M. Sc.* **220**:316-338, 1950.
6. Theiler, M., and Smith, H. H. Effect of prolonged cultivation in vitro upon pathogenicity of yellow fever virus. *J. Exper. Med.* **65**: 767-786, 1937.
7. Maitland, H. B., and Maitland, M. C. Cultivation of vaccinia virus without tissue culture. *Lancet* **2**:596, 1928.
8. Smith, W. M., Chambers, V. C., and Evans, C. A. Growth of neurotropic viruses in extraneural tissues: preliminary report on propagation of poliomyelitis virus (Lansing and Hof. strains) in cultures of human testicular tissue. *Northwest Med.* **49**:368-373, 1950.
9. Syverton, J. T., Scherer, W. F., and Butorac, G. Propagation of poliomyelitis virus in cultures of monkey and human testicular tissues. *Proc. Soc. Exper. Biol. & Med.* **77**:23-28, 1951.
10. Weller, T. H., Enders, J. F., Robbins, F. C., and Stoddard, M. B. Studies on cultivation of poliomyelitis viruses in tissue culture. I. Propagation of poliomyelitis viruses in suspended cell cultures of various human tissues. *J. Immunol.* **69**:645-671, 1952.
11. Robbins, F. C., Weller, T. H., and Enders, J. F. Studies on cultivation of poliomyelitis viruses in tissue culture. II. Propagation of poliomyelitis viruses in roller tube cultures of various human tissues. *J. Immunol.* **69**:673-694, 1952.
12. Gey, G. O., and Bang, F. B. Experimental studies on cultural behavior and infectivity of lymphopathia venerea virus maintained in tissue culture. *Bull. Johns Hopkins Hosp.* **68**:393-417, 1939.
13. Svedmyr, A., Enders, J. F., and Holloway, A. Complement fixation with three types of poliomyelitis viruses propagated in tissue culture. *Am. J. Hyg.* **57**:60-70, 1953.
14. Wood, W., Franklin, A. E., Clark, E. M., Duncan, D., and Rhodes, A. J. Cultivation of poliomyelitis virus in tissue culture. III. Synthetic medium in roller tube cultures. *Proc. Soc. Exper. Biol. & Med.* **81**:434-438, 1952.
15. Fischer, A. Application of soybean inhibitor in tissue cultivation. *Science* **109**:611, 1949.
16. Morgan, J. F., and Parker, R. C. Use of antitryptic agents in tissue culture. I. Crude soybean trypsin inhibitor. *Proc. Soc. Exper. Biol. & Med.* **71**:665-668, 1949.
17. Hanks, J. H., and Wallace, R. E. Relation of oxygen and temperature in preservation of tissues by refrigeration. *Proc. Soc. Exper. Biol. & Med.* **71**:196-200, 1949.
18. Enders, J. F. Bovine amniotic fluid as tissue culture medium in cultivation of poliomyelitis and other viruses. *Proc. Soc. Exper. Biol. & Med.* **82**:100-105, 1953.
19. Simms, H. S., and Sanders, M. Use of serum ultrafiltrate in tissue cultures for studying deposition of fat and for propagation of viruses. *Arch. Path.* **33**:619-635, 1942.
20. Landsteiner, K., and Popper, E. Übertragung der Poliomyelitis acuta auf Affen. *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **2**:377-390, 1909.
21. Paul, J. R. Poliomyelitis. In *Diagnostic Procedures for Virus and Rickettsial Diseases*. 347 pp. New York City: American Public Health Association, 1948. Pp. 165-186.
22. Armstrong, C. Experimental transmission of poliomyelitis to eastern cotton rat, Sigmodon hispidus hispidus. *Pub. Health Rep.* **54**: 1719-1721, 1939.
23. Paul, J. R. Knowledge and trends in poliomyelitis: summary. In *Poliomyelitis*. Papers and discussions presented at the Second International Poliomyelitis Conference, Copenhagen, Denmark, September, 1951. 555 pp. Philadelphia: Lippincott, 1952. Pp. 376-381.
24. Burnet, F. M., and Macnamara, J. Immunological differences between strains of poliomyelitic virus. *Brit. J. Exper. Path.* **12**:57-61, 1931.
25. Committee on Typing of the National Foundation for Infantile Paralysis. Immunologic classification of poliomyelitis viruses. V. Discussion of results and general summary. *Am. J. Hyg.* **54**: 268-274, 1951.
26. Horstmann, D. M. Poliomyelitis virus in blood of orally infected monkeys and chimpanzees. *Proc. Soc. Exper. Biol. & Med.* **79**:417-419, 1952.
27. Bodian, D. Reconsideration of pathogenesis of poliomyelitis. *Am. J. Hyg.* **55**:414-438, 1952.
28. Sabin, A. B., and Olitsky, P. K. Cultivation of poliomyelitis virus in vitro in human embryonic nervous tissue. *Proc. Soc. Exper. Biol. & Med.* **34**:357-359, 1936.
29. Burnet, F. M., and Jackson, A. V. Poliomyelitis: spread of poliomyelitis virus in cynomolgus monkeys with particular reference to infection by pharyngeal-intestinal route. *Australian J. Exper. Biol. & M. Sc.* **18**:361-366, 1940.
30. Weller, T. H., and Enders, J. F. Production of hemagglutinin by mumps and influenza A viruses in suspended cell tissue cultures. *Proc. Soc. Exper. Biol. & Med.* **69**:124-128, 1948.
31. Weller, T. H., and Stoddard, M. B. Intranuclear inclusion bodies in cultures of human tissue inoculated with varicella vesicle fluid. *J. Immunol.* **68**:311-319, 1952.
32. Milzer, A., Levinson, S. O., Vanderboom, K., and Adelman, P. Cultivation of poliomyelitis virus (Lansing strain) in human embryonic and placental tissues. *Proc. Soc. Exper. Biol. & Med.* **74**: 136-138, 1950.
33. Huang, C. H. Further studies on titration and neutralization of western strain of equine encephalomyelitis virus in tissue culture. *J. Exper. Med.* **78**:111-126, 1943.
34. Robbins, F. C., Enders, J. F., and Weller, T. H. Cytopathogenic effect of poliomyelitis viruses in vitro on human embryonic tissues. *Proc. Soc. Exper. Biol. & Med.* **75**:370-374, 1950.
35. Feller, A. E., Enders, J. F., and Weller, T. H. Prolonged coexistence of vaccinia virus in high titre and living cells in roller tube cultures of minced embryonic tissues. *J. Exper. Med.* **72**:367-388, 1940.
36. Robbins, F. C., Enders, J. F., Weller, T. H., and Florentino, G. L. Studies on cultivation of poliomyelitis viruses in tissue culture. V. Direct isolation and serologic identification of virus strains in tissue culture from patients with nonparalytic and paralytic poliomyelitis. *Am. J. Hyg.* **54**:286-293, 1951.
37. Riordan, J. T., Ledinko, N., and Melnick, J. L. Multiplication of poliomyelitis viruses in tissue cultures of monkey testes. II. Direct isolation and typing of strains from human stools and spinal cords in roller tubes. *Am. J. Hyg.* **55**:339-346, 1952.
38. Youngner, J. S., Lewis, L. J., Ward, E. N., and Salk, J. E. Studies on poliomyelitis viruses in cultures of monkey testicular tissue. III. Isolation and immunologic identification of poliomyelitis viruses from fecal specimens by means of roller tube cultures. *Am. J. Hyg.* **55**:347-356, 1952.
39. Syverton, J. T., and Scherer, W. F. Studies on propagation in vitro of poliomyelitis viruses. I. Viral multiplication in tissue cultures employing monkey and human testicular cells. *J. Exper. Med.* **96**:355-367, 1952.
40. Melnick, J. L., and Riordan, J. T. Poliomyelitis viruses in tissue culture. IV. Protein free nutrient media in stationary and roller tube cultures. *Proc. Soc. Exper. Biol. & Med.* **81**:208-213, 1952.
41. Franklin, A. E., Duncan, D., Wood, W., and Rhodes, A. J. Cultivation of Lansing poliomyelitis virus in tissue culture. II. Utilization of glucose in synthetic medium. *Proc. Soc. Exper. Biol. & Med.* **79**:715-718, 1952.
42. Smith, W. M., Chambers, V. C., and Evans, C. A. Growth of neurotropic viruses in extraneural tissues. IV. Poliomyelitis virus in human testicular tissue *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **76**:696-700, 1951.
43. Youngner, J. S., Ward, E. N., and Salk, J. E. Studies on poliomyelitis viruses in cultures of monkey testicular tissue. I. Propagation of virus in roller tubes. *Am. J. Hyg.* **55**:291-300, 1952.
44. Ledinko, N., Riordan, J. T., and Melnick, J. L. Multiplication of poliomyelitis viruses in tissue cultures of monkey testes. I. Growth curves of Type 1 (Brunhilde) and Type 2 (Lansing) strains and desription of quantitative neutralization test. *Am. J. Hyg.* **55**: 323-358, 1952.
45. Salk, J. E., Bennett, B. L., Lewis, L. J., Ward, E. N., and Youngner, J. S. Studies in human subjects on active immunization against poliomyelitis. I. Preliminary report of experiments in progress. *J. A. M. A.* **151**:1081-1098, 1953.
46. Ledinko, N., and Melnick, J. L. Poliomyelitis viruses in tissue culture. III. Susceptibility of testicular tissue from immune monkeys. *Proc. Soc. Exper. Biol. & Med.* **81**:144-149, 1952.
47. Scherer, W. F., Syverton, J. T. and Gey, G. O. Propagation *in vitro* of poliomyelitis viruses in cultures of human epithelial cells (strain Hela, Gey) derived from carcinoma of cervix. *Federation Proc.* **12**:457, 1953.
48. Morgan, J. F., Morton, H. J. and Parker, R. C. Nutrition of animal cells in tissue culture. Initial studies on synthetic medium. *Proc. Soc. Exper. Biol. & Med.* **73**:1-8, 1950.
49. Thicke, J. C., Duncan, D., Wood, W., Franklin, A. E. and Rhodes, A. J. Cultivation of poliomyelitis virus in tissue culture. I. Growth of Lansing strain in human embryonic tissue. *Canad. J. M. Sc.* **30**: 231-245, 1952.
50. Svedmyr, A., Enders, J. F., and Holloway, A. Complement fixation with Brunhilde and Lansing poliomyelitis viruses propagated in tissue culture. *Proc. Soc. Exper. Biol. & Med.* **79**:296-300, 1952.
51. Seibert, F. B. Chemical composition of active principle of tuberculin. XI. Improved and simplified method for making standard undenatured tuberculin of any desired strength and method of chemical assay. *J. Biol. Chem.* **78**:345-362, 1928.
52. Fulton, F. and Dumbell, K. R. Serological comparison of strains of influenza virus. *J. Gen. Microbiol.* **3**:97-111, 1949.
53. Enders, J. F. Unpublished data.
54. Franklin, A. E., Duncan, D., Wood, W., and Rhodes, A. J. Cultivation of poliomyelitis virus in tissue culture. IV. Further observations on virus propagation in human tissues with synthetic nutrient medium. *Canad. J. M. Sc.* **31**:64-74, 1953.
55. Duncan, D., Franklin, A. E., Wood, W., and Rhodes, A. J. Cultivation of poliomyelitis virus in tissue culture. V. Observations on virus propagation in certain animal tissues with synthetic nutrient medium. *Canad. J. M. Sc.* **31**:75-83, 1953.
56. Enders, J. F., Robbins, F. C., and Weller, T. H. Unpublished data.
57. Scherer, W. F., and Syverton, J. T. Studies on propagation in vitro of poliomyelitis viruses. III. Propagation of poliomyelitis viruses in tissue cultures devoid of nerve cells. *J. Exper. Med.* **96**:389-400, 1952.

58. Brown, G. C., Ackermann, W. W., and Schiebl, J. H. Effect of DL-ethionine on poliomyelitis virus growth in tissue culture. *Proc. Soc. Exper. Biol. & Med.* 77:367-369, 1951.

59. Scherer, W. F., and Syverton, J. T. Studies on propagation in vitro of poliomyelitis viruses. II. Description of growth curve and its relation to cytopathogenicity of poliomyelitis virus. *J. Exper. Med.* 96:369-388, 1952.

60. Brown, G. C. Influence of chemicals on propagation of poliomyelitis in tissue culture. *Federation Proc.* 11:463, 1952.

61. Brown, G. C., and Craig, D. E. Effect of benzimidazole on experimental poliomyelitis in mice and monkeys. *Federation Proc.* 12: 437, 1953.

62. Ledinko, N., Riordan, J. T., and Melnick, J. L. Differences in cellular pathogenicity of two immunologically related poliomyelitis viruses as revealed in tissue culture. *Proc. Soc. Exper. Biol. & Med.* 78: 83-88, 1951.

63. Youngner, J. S., Ward, E. N., and Salk, J. E. Studies on poliomyelitis viruses in cultures of monkey testicular tissue. II. Differences among strains in tissue culture infectivity with preliminary data on quantitative estimation of virus and antibody. *Am. J. Hyg.* 56:301-322, 1952.

64. Enders, J. F., Weller, T. H., and Robbins, F. C. Alteration in pathogenicity for monkeys of Brunhilde strain of poliomyelitis virus following cultivation in human tissues. *Federation Proc.* 11:467, 1952.

65. Roca-Garcia, M., Moyer, A. W., and Cox, H. R. Poliomyelitis. II. Propagation of MEFI strain of poliomyelitis virus in developing chick embryo by yolk sac inoculation. *Proc. Soc. Exper. Biol. & Med.* 81:519-525, 1952.

66. Cabasso, V. J., Stebbins, M. R., Dutcher, R. M., Moyer, A. W., and Cox, H. R. Poliomyelitis. III. Propagation of MEFI strain of poliomyelitis virus in developing chick embryo by allantoic cavity inoculation. *Proc. Soc. Exper. Biol. & Med.* 81:525-529, 1952.

67. Ledinko, N. Interference between poliomyelitis viruses in tissue culture. *Federation Proc.* 12:451, 1953.

68. Weller, T. H., Robbins, F. C., Stoddard, M. B. and Florentino, G. L. Propagation of Coxsackie viruses in cultures of human tissues. *J. Immunol.* (in press).

69. Melnick, J. L., Riordan, J. T., Cornen, E. C., and Macrae, A. D. Tissue-culture pathogenic agents other than poliomyelitis virus isolated from cases of suspected poliomyelitis. *Federation Proc.* 12:454, 1953.

70. Kibrick, S. and Enders, J. F. Unpublished data.

71. Syverton, J. T., and Scherer, W. F. Utilization of stable strain of human epithelial cells (Hela, Gey) for diagnosis of poliomyelitis. *Federation Proc.* 12:462, 1953.

72. Weller, T. H., Enders, J. F., Robbins, F. C., Stoddard, M. B. and Florentino, G. L. Unpublished data.

73. Bodian, D., and Paffenbarger, R. S., Jr. Viremia and antibody response of abortive poliomyelitis cases. *Federation Proc.* 12:457, 1953.

74. Enders, J. F. Multiplication and properties of poliomyelitis viruses in cultures of human tissue. In *Poliomyelitis*, Papers and discussions presented at the Second International Poliomyelitis Conference, Copenhagen, Denmark, September, 1951. 555 pp. Philadelphia: Lippincott, 1952. Pp. 33-43.

75. Salk, J. E., Lewis, L. J., Bennett, B. L., and Youngner, J. S. Immunization of monkeys with poliomyelitis viruses grown in cultures of monkey testicular tissue. *Federation Proc.* 11: 480, 1952.

76. Contreras, G., Barnett, V. H., and Melnick, J. L. Identification of Coxsackie viruses by immunological methods and their classification into 16 antigenically distinct types. *J. Immunol.* 69:395-414, 1952.

77. Robbins, F. C., Enders, J. F., and Kibrick, S. Unpublished data.

78. Sabin, A. B., and Steigman, A. J. Poliomyelitis virus of low virulence in patients with epidemic "summer grippe or sore throat." *Am. J. Hyg.* 49:176-193, 1949.

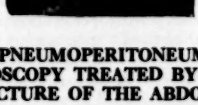
79. Steigman, A. J., and Kokko, U. P. Immunologically unclassified human virus (Mack) having some properties of poliomyelitis. *Federation Proc.* 12:461, 1953.

80. Committee on Nomenclature of the National Foundation for Infantile Paralysis. Proposed provisional definition of poliomyelitis virus. *Science* 108:701-705, 1948.

81. Weller, T. H. Serial propagation in vitro of agents producing inclusion bodies derived from varicella and herpes zoster. *Proc. Soc. Exper. Biol. & Med.* (in press).

82. Neva, F. A. Unpublished data.

MEDICAL INTELLIGENCE



MASSIVE PNEUMOPERITONEUM DURING GASTROSCOPY TREATED BY NEEDLE PUNCTURE OF THE ABDOMEN

EMANUEL M. RAPPAPORT, M.D.,* AND SIDNEY FINKEL, M.D.†

JAMAICA, NEW YORK

GASTROSCOPY with the flexible, finger-tip instrument is, as a rule, an innocuous diagnostic procedure. The sudden onset of pneumoperitoneum during the course of this examination, however, is a complication that is usually distressing to the patient and alarming to the examiner. Although occasionally the condition is unsuspected until the examination has been concluded, usually the gastroscopist is immediately apprised of the accident by his inability to inflate the stomach with air or by the collapse of the stomach that had been inflated. Simultaneously, the abdomen becomes distended and tympanitic, with loss of liver dullness. The discomfort of the patient varies with the quantity of air insufflated into the peritoneal cavity. At times pneumoperitoneum may be associated with mediastinal, scrotal or even cervical emphysema.

It seems obvious that pneumoperitoneum during gastroscopy results from perforation of the stomach. Nevertheless, there have been repeated accounts of this complication without the demonstration of a visceral perforation on careful inspection of the stomach at laparotomy.

Schindler[1] and Berk[2] reported the inability of the surgeon to find a free perforation of the stomach in patients operated on shortly after pneumoperitoneum sustained during gastroscopy. In 1947 Chamberlin[3] recounted a similar fruitless search for a gastric perforation. He concluded that if faced with a similar situation he would deflate the abdomen by needle puncture and await further signs of perforation before subjecting the patient to operation. However, subsequent reports[4-6] cited surgical exploration for suspected gastric perforations that were not found.

The case presented below is the first recorded in which the method recommended by Chamberlin[3] was employed. The excellent result obtained by this simple measure suggests that it is the therapeutic procedure of choice for this complication and confirms his opinion that operation is not always indicated.

CASE REPORT

A 74-year-old woman was admitted to the hospital on March 21, 1951, because of intermittent diarrhea of 1 month's duration. The temperature, pulse and respirations were normal;

*Associate visiting physician and physician-in-charge, Gastro-Intestinal Outpatient Department, Queens General Hospital.

†Formerly, resident in medicine, Queens General Hospital.

the blood pressure was 90/60. There was slight epigastric tenderness but no palpable masses.

X-ray and gastroscopic examinations showed a small gastric ulcer on the lesser curvature of the prepyloric region. It was interpreted as a benign lesion despite the fact that repeated gastric analyses with histamine revealed absence of free hydrochloric acid. After 6 weeks on an ulcer diet without antacids the ulcer could no longer be visualized on x-ray examination. Gastroscopic study was repeated on June 9. Some resistance was encountered in the passage of the instrument through the cardia but the stomach was entered and inflated. The gastric mucosa was seen only momentarily, and then the stomach collapsed. Simultaneously, the patient complained of excruciating abdominal pain. The abdomen became markedly distended and tense, and since the light of the instrument could be seen through the abdominal wall it was obvious that a pneumoperitoneum had occurred; accordingly, the instrument was withdrawn.

The patient became markedly dyspneic and cyanotic, with a rapid, feeble pulse, and writhed in pain. Since the immediate problem was the relief of pain and respiratory embarrassment from massive pneumoperitoneum, an area midway between the umbilicus and the anterior superior spine of the iliac crest was infiltrated with 1 per cent procaine, and a needle passed into the peritoneal cavity. Air escaped through the needle with a hiss, and the abdomen was slowly deflated. The needle was withdrawn when the hissing sound stopped although a considerable amount of air remained in the abdomen, since liver dullness remained obliterated. The pain diminished considerably, and the pulse and respirations improved.

FIGURE 1. *X-ray Film of the Abdomen, Showing Massive Pneumoperitoneum Still Present Twenty-Four Hours after Gastroscopy. Despite the large quantity of air in the abdomen the patient was quite comfortable.*

Penicillin was administered in doses of 300,000 units every 4 hours. She was fed parenterally for 48 hours, during which the abdomen was generally tender but soft and the temperature and pulse remained normal. She refused to permit the passage of a Levin tube for gastric suction. A film of the abdomen taken in the erect position 24 hours after gastroscopy still showed considerable air under both leaves of the diaphragm (Fig. 1). Since she was comfortable no attempt was made to withdraw more air from the abdomen. Liquid feedings were well tolerated after 2 days, and subsequent recovery was uneventful. She was discharged on July 15, and has been followed for 16 months on the hospital home-care program, during which she has had no gastrointestinal complaints.

Discussion

The mechanism of massive pneumoperitoneum during gastroscopy without demonstrable visceral perforation is still a matter of conjecture. Schindler[1] believed that in his case a tiny perforation of the stomach had occurred and had sealed off and thus could not be demonstrated three hours later at operation. Chamberlin[2] believed that the air in the peritoneal cavity had diffused through the thin base of the gastric ulcer that was present in his case. Fierst, Robinson and Lasagna[6] suggested that with increased intragastric pressure from spasm of the cardia or pylorus, air may be forced into the perivascular sheaths through a weak point in the mucosa. On reaching the serosa the air readily dissects along the peritoneal reflections of the stomach, forming large vesicles, which rupture and thus account for the pneumoperitoneum without a gastric perforation.

However, if pylorospasm or weak points in the stomach wall predisposed to this complication gastroscopy would be a hazardous procedure in patients with large gastric ulcers or pyloric obstruction. Actually, its rarity is indicated by the fact that the case reported above is the first observed in over 3000 gastroscopic examinations.

The excellent response to needle puncture of the abdomen in this patient, who experienced extreme symptoms, indicates that this conservative measure should be employed when the pneumoperitoneum is massive. Even this would be unnecessary in a patient with few associated symptoms. Surgical intervention is apparently indicated in few cases and then only after clinical observations indicate that a visceral perforation exists. Since gastroscopy is always performed on a fasting patient the danger of leakage from a tiny perforation is less serious than it would be from a spontaneous perforation.

Summary

A case of massive pneumoperitoneum occurring during gastroscopy is presented. Deflation of the abdomen by needle puncture was followed by uneventful recovery.

Since a visceral perforation has not been demonstrable in other cases of this type, an initial trial of such conservative management appears indicated for this complication.

148-25 89 Avenue

References

1. Schindler, R. Passage of air through gastric wall during gastroscopy with no wound demonstrable three hours later. *Gastroenterology* 5: 34-36, 1945.
2. Berk, J. E. Pneumoperitoneum following gastroscopy without evidence of perforation at laparotomy fourteen hours later. *Gastroenterology* 6:218, 1946.
3. Chamberlin, D. T. Pneumoperitoneum following gastroscopy apparently without perforation. *New Eng. J. Med.* 237:843-845, 1947.
4. Lichtstein, J., and Wharton, G. K. Gastroscopy followed by pneumoperitoneum with no discernible lesion at laparotomy three hours later. *Gastroenterology* 11:127-129, 1948.
5. Gilbert, R. L., Knight, W. A., Jr., and Dalton, A. R. Pneumoperitoneum following gastroscopy without demonstrable perforation at laparotomy. *Gastroenterology* 12:139-141, 1949.
6. Fierst, S. M., Robinson, H. M., and Lasagna, L. Interstitial gastric emphysema following gastroscopy; its relation to syndrome of pneumoperitoneum and generalized emphysema with no evident perforation. *Ann. Int. Med.* 34:1202-1212, 1951.

BY THE LONDON POST

The Royal Touch

JOHN LISTER, M.D.

LONDON, ENGLAND

CORONATION year has brought expressions of loyalty to the Crown from all sections of the community, and the medical profession has not been backward in paying its own homage. Many journals have published coronation issues, and these have recalled in special articles the long-standing royal patronage of the profession and the keen interest that many monarchs have taken in the health of their people.

E. Ashworth Underwood, in an article in the *British Medical Journal*, Coronation Number,* traces the relation between the Crown and medicine. He describes how St. Bartholomew's, the oldest London hospital and dating from 1123, came into being through the generosity of King Henry I. The Augustinian monk, Rahere, traveled from England to Rome, where he had a vision in which the apostle St. Bartholomew instructed him to "found at Smithfield a Tabernacle of the Lamp, a temple of the Holy Ghost." On his return to London he found that this site in Smithfield was owned by the King, who was, however, gracious enough to allow the monk to build a priory upon it with a hospital attached. Since the time of its early foundation, St. Bartholomew's has always cared for the "sick poor," and to the present day each new intern is reminded of this when he is given his "charge" concerning his duties.

After the dissolution of the monasteries Henry VIII took the revenue of St. Bartholomew's priory into his own hands and granted royal charters, under the terms of which the hospital is still chiefly administered.

It was also during the reign of Henry VIII that a certain organization of the medical profession took place. Surgery, medicine and the art of the apothecary had not previously been clearly differentiated, and quackery was rife. Thomas Linacre, physician to the King, was anxious for reform and was instrumental in framing an act of Parliament providing that no one should practice medicine within the City of London without passing an examination conducted by the Bishop of London or the Dean of St. Paul's. Six years later, in 1518, the King founded the College of Physicians, of which Linacre became the first president and to whose influence the foundation was largely due. The surgeons also became recognized during the same reign, and Thomas Vicary, who treated the king for varicose ulcers with temporary success, was largely responsible for the act of Parliament of 1540, which united the barbers and the surgeons in the Barber-Surgeon Company.

So it was that when Queen Elizabeth I ascended the throne in 1558, the physicians were just ceasing to be under the influence of the Church and the surgeons had been elevated to the dignity of a profession, but the apothecaries were still associated with the grocers. This last was the cause of much hard feeling. The physicians complained that the apothecaries not only compounded drugs but also saw patients; the apothecaries complained that the physicians not only saw patients but also compounded drugs, and the grocers complained that the apothecaries sold not only drugs but also groceries. The apothecaries sought a remedy to the dispute by asking for a monopoly in the compounding and selling of drugs, but in spite of their representations, Queen Elizabeth I, in 1588, refused to grant them their request. (I cannot help wondering whether this is why in this country the American drugstore is facetiously described as that wonderful place where one can buy anything except drugs.)

In any event, medicine progressed greatly in the days of Henry VIII and Elizabeth I, and through many successive reigns the medical profession has received the sovereign's encouragement and patronage. It is particularly appropriate to recall at this coronation time, the practice known as the Royal Touch. As L. A. Underwood again states, the gift of healing by touching with hands was supposed to be conferred on the sovereign at his coronation. The practice dates in this country from 1066, when the king "cured an affected girl." The disease most commonly treated by touching was scrofula or tuberculous cervical lymphadenitis, but patients suffering from other conditions were also brought for treatment. King Henry VII made the practice a religious ceremony and gave each patient a golden "angel," which was hung around the neck. Charles II is said to have touched 90,000 persons in nineteen years, and Pepys has described the religious ceremony as carried out in his day. Queen Anne used the practice as a means to demonstrate her hereditary right to the throne, and Samuel Johnson was among her patients when he was brought as a child of two and a half years, with tuberculous lymph nodes in the neck. The custom finally disappeared on the accession of George I, and since that time the sovereign's interest in the people's health has become based on the sound scientific advances of modern times. In this respect, it seems fitting that in the month before Queen Elizabeth II was crowned, she laid the memorial stone of the new Royal College of Surgeons in Lincoln's Inn Fields. Much of the college was destroyed by enemy action in 1941, and the new building is designed to enlarge the institution to accommodate all its scientific and educational activities. At the ceremonial laying of the

*Underwood, E. A. Medicine and crown. *Brit. M. J.* 1:1185-1191, 1953.

stone, Sir Cecil Wakeley, president of the College, said that the great hall would be the heart of the new college, where its scientific and social meetings would be held. Above the hall there would be three new floors to accommodate laboratories and museums, and, at a later stage, a new residential block is to be built by the generosity of the Nuffield Trust, chiefly for overseas students. Perhaps the Queen's laying of the foundation stone of this great new project in her coronation year may be regarded as a contemporary Royal Touch, from which it may be hoped that many thousands far from Lincoln's Inn Fields will derive benefit.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39311

PRESENTATION OF CASE

First admission. A sixty-five-year-old mentally retarded widow was admitted to the hospital complaining of increasing shortness of breath.

Three years previously dyspnea, orthopnea, ankle edema and intermittent discomfort across the chest relieved by nitroglycerin, had first developed. For these symptoms she was treated at another hospital for several months with digitalis and mercurial diuretics. After discharge she took digitalis and mercurial diuretics intermittently and remained active and well. Four or five months before admission an x-ray film of the chest demonstrated cardiac enlargement of moderate degree, chiefly of the left ventricle, and congestive changes in both lungs (Fig. 1). Two months before admission, when she was admitted to a second hospital because of pneumonia of the right upper lobe due to a Type 14 pneumococcus, she was told that she had "rheumatic heart disease with a leaky valve." On examination an aortic diastolic murmur was heard, and the spleen was palpable 5 cm. below the left costal margin. Treatment consisted of digitalis, mercurial diuretics, antibiotics and nitroglycerin. At this time because of recent night sweats, fever, anorexia and cough, tuberculosis was considered, but studies were negative. Five days before admission, after a mild upper respiratory infection, the symptoms of cough dyspnea, edema and orthopnea recurred, and it was necessary for her to sleep in a chair. There were no chills, fever, chest pain or hemoptysis. She had omitted the digitalis for four days before entry.

At the age of ten the patient had had an episode of swollen, painful knees and ankles associated with fever and was told that she had rheumatic fever. At twenty-five years of age, during her only pregnancy, she had poliomyelitis, which left her with a shortened right leg. At the age of thirty-five, while living in Rhode Island, she had "malaria." At the age of fifty-one she passed 2 small kidney stones. She denied syphilis and claimed to have had 6 negative blood tests.

Physical examination showed a slightly pale and alert woman with mild dyspnea. The neck veins were pulsating but not distended. There was a left lateral thoracolumbar scoliosis with a dorsal kyphosis and an increased anteroposterior diameter of the chest. A loud pleural friction rub was heard over the right middle lobe anteriorly, and breath sounds were decreased at the right base. There was no dullness. Bubbling rales were present at both lung bases. The heart was enlarged, the border of cardiac dullness extending to the anterior axillary line on the left. The rhythm was irregular, and the pulmonic second sound was louder than the aortic. The following murmurs were heard: a Grade 1 aortic systolic, a Grade 2 to 3 aortic diastolic along the left sternal border, a Grade 2 apical systolic and a questionable mid-diastolic rumble at the apex. There were no thrills, but capillary pulsations and a Corrigan pulse were present. Both the liver and the spleen were palpable 2 fingerbreadths below the respective costal margins. There was a +++ pitting edema of the ankles and mild cyanosis of the nail beds.

The temperature was normal, the pulse 108 and irregular, and the respirations 28. The blood pressure was 160 systolic, 70 diastolic.

Urine specimens had a maximum specific gravity of 1.019 and gave + to ++ tests for albumin; after the first week of hospitalization the sediment contained 10 to 20 red cells, 2 to 10 white cells and occasional granular and hyaline casts per high-power field. A urine culture was negative. The blood hemoglobin was 11 gm. per 100 cc. and the white-cell count on admission was 19,000, with 80 per cent neutrophils and 20 per cent lymphocytes. Thereafter, the white-cell count was normal, with 80 per cent neutrophils and 16 per cent lymphocytes on one occasion. The total protein was 7.54 gm., the albumin 3.36 gm. and the globulin 4.18 gm. per 100 cc. A bromsulfalein test was negative, as was the blood Hinton reaction. A throat culture grew out alpha-hemolytic and nonhemolytic streptococci and a few diphtheroids. The prothrom-

bin time was 14 seconds (normal, 13 seconds). The nonprotein nitrogen on admission was normal but rose on the eighth hospital day to 68 mg. and on the thirteenth day to 100 mg. per 100 cc., falling on the fifteenth day to 50 mg. per 100 cc. On the fifteenth hospital day the serum chloride rose to 119 milliequiv. per liter; the carbon dioxide was 10.0 milliequiv. per liter. An electrocardiogram on admission showed auricular fibrillation with

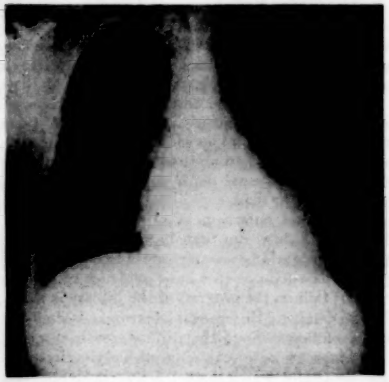


FIGURE 1. *Roentgenogram of the Chest Sixteen Months before the Final Admission, Showing Evidence of Ventricular Enlargement and Pulmonary Congestion.*

nonspecific T-wave changes, including T-wave inversion over the precordium. A roentgenogram of the chest on admission revealed a large amount of density in the anterior segment of the right upper lobe (Fig. 2). There were also considerable densities elsewhere in both lungs, particularly in the central portions. The heart was moderately enlarged, and there was some fluid in the right pleural cavity. Three days later a second chest film demonstrated a linear density in the right-lower-lung field. The heart shadow was enlarged chiefly to the left, and the cardiac thoracic ratio was 14:24 cm. There appeared to be enlargement of the left ventricle and possibly of the right. The left atrium was not definitely enlarged. The right leaf of the diaphragm moved less well than the left. The spleen appeared quite large. A barium-swallow examination and gastrointestinal series were not remarkable.

In the hospital the patient had occasional temperature elevations to 101°F. She was treated with oxygen, ammonium chloride, digitoxin, crysticillin and Mercuhydrin. On this regimen, by the fourth hospital day the lungs were clear, the legs reduced in size and nontender, and she reverted to a normal sinus rhythm, although the murmurs remained unchanged. Dicumarol therapy was started on the second hospital day but was discontinued after four days because of apparent sensitivity. She was discharged three weeks after entry on a low-salt diet, digitalis, 0.1 gm. every other day, Mercuhydrin, 1 cc. intramuscularly every week, and nitroglycerin as needed for occasional chest pains.

She was followed in the Medical Clinic at monthly intervals and was doing fairly well with occasional ankle edema and fine basal rales in the lungs. A urea clearance test showed a maximum clearance

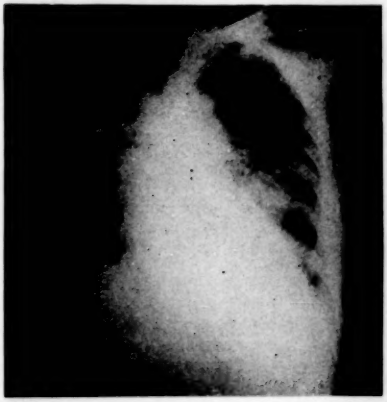


FIGURE 2. *Roentgenogram of the Chest at the Time of the First Admission, Showing the Homogeneous Density in the Right Upper Lobe.*
This had completely disappeared in a film taken four days later.

of 27 per cent. An electrocardiogram disclosed a normal sinus rhythm, with nonspecific changes in the ST segment and T waves. She was last seen five months before the second admission. A roentgenogram of the chest taken two months after discharge while the patient was being followed in the Out-Patient Department showed evidence of congestive heart failure (Fig. 3).

Final admission (nine months after first admission). The patient was admitted to the Emergency Ward complaining of severe chest pain. She was unable to give a coherent history, but according to the family she had been fairly well until three months prior to entry, when a chronic cough and occasional chest pain developed. These symptoms continued, and for the three or four weeks before admission she had had nightly shaking chills and sweats, with chest and side pain and marked dys-

pnea. During this period she was forced to sleep sitting in a chair and had frequent episodes of paroxysmal nocturnal dyspnea. She had had no dysuria, hematuria or melena.

On examination she was in acute respiratory distress, sweating profusely, cold, clammy and cyanotic. She was incontinent of urine and feces. The neck veins were distended to the jaw and pulsating. There were fine rales at the lung bases but no dullness. The heart was enlarged, with an irregular rhythm and a definite gallop, but sounds were difficult to hear because of the labored respirations. The liver edge was palpable 4 fingerbreadths below the right costal margin and was very tender.

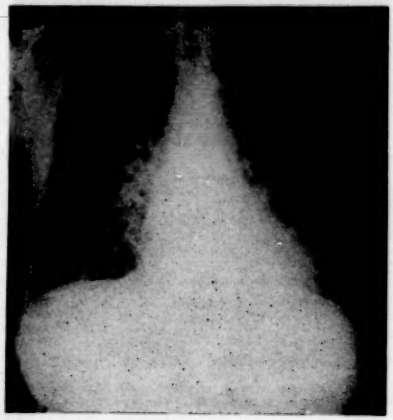


FIGURE 3. *Roentgenogram of the Chest, Showing Evidence of Fairly Severe Bilateral Congestive Heart Failure.*

There was + to ++ edema and excoriations of both legs.

The temperature was 100°F., the pulse 72 and irregular, and the respirations 35. The blood pressure was 75 systolic, 45 diastolic.

Examination of the blood showed a hemoglobin of 11.0 gm. per 100 cc. and a white-cell count of 12,500, with 75 per cent neutrophils. An electrocardiogram was consistent with a posterior myocardial infarction.

In the hospital she was treated with Cedilanid, oxygen, morphine, epinephrine and Mercuhydrin. Ten hours after entry the chest was clear, respirations were 30 per minute, and she appeared to be improving; however, an hour later she suddenly died.

DIFFERENTIAL DIAGNOSIS

DR. MYLES P. BAKER*: This is the story of two successive hospital admissions of a sixty-five-year-old patient, with the murmur of valvular heart disease and the story of congestive heart failure, who finally entered the hospital in a state of circulatory collapse with electrocardiographic evidence of posterior myocardial infarction and died suddenly. Certain unusual features about this case stand out in the history. Can I assume that this woman had rheumatic heart disease with aortic regurgitation? I think I can. It is highly unlikely that she had syphilitic aortitis with aortic regurgitation on that basis because the serologic test was negative. In about 80 per cent of cases of syphilitic aortitis the test is positive. I think some twenty years ago in a series of such cases reported at Johns Hopkins Hospital the figure given was somewhat higher than that. Secondly, auricular fibrillation is unusual with aortic regurgitation. Moreover, if she had syphilitic aortitis, aortic regurgitation and enlargement of the left ventricle, with heart failure on that basis beginning three years before death, her course would have been more rapid. Once such patients have evidence of congestive heart failure, the progress of the disease is rapid.

To go back to the unusual features, I shall list them as follows: first, the diffuse densities noted in the lungs by x-ray examination on the first hospital admission, which do not sound in description like the typical picture of congestive heart failure; secondly, fever, which she had before the first admission and during the first three weeks of the first hospitalization, and which for the month before admission had been suggested in a sense by the frequent chills; and, thirdly, the hyperglobulinemia described once. Was that repeated?

DR. ROBERT H. FENNELL, JR.: No, it was not.

DR. BAKER: I should think one should find out whether the determination would have been the same twice. Two other unusual features were the splenomegaly and the appearance of renal insufficiency in the second week of the hospital stay at a time when the congestive heart failure apparently was improving. Those findings require some explanation. I think I had better ask Dr. Wyman to show the x-ray films because a good deal depends on their appearance.

DR. STANLEY M. WYMAN: The initial examination of the chest, sixteen months before the final admission, shows the cardiac enlargement very well (Fig. 1). There is enlargement of the left ventricle and very possibly of the right ventricle. I do think there is evidence for saying that the left atrium is definitely enlarged. The hilar and central pulmonary vascular shadows are increased in prominence, consistent with a chronic degree of pulmonary congestion. I do not see any

*Physician, Massachusetts General Hospital.

intracardiac calcification, but this might be overlooked on films and is best seen at fluoroscopy. The next examination is the reportedly negative gastrointestinal series, which I think is not unusual. I cannot exclude tiny varices, but I do not think they are present. There is a small hiatus hernia, but I doubt if it is significant. The next examination of the chest, done during the first admission about six months after the original examination, demonstrates the large density described in the right-lung field (Fig. 2). This is an area of homogeneous density, which lies in the upper lobe and may represent some form of consolidation. There is, however, a diffuse increase in density throughout both lungs lying chiefly centrally that is more universal than the density in the upper-lung field already described.

DR. BAKER: That first film must have been taken elsewhere before the first hospital admission — that is, two months before the patient had gone into the other hospital and the diagnosis of pneumococcal pneumonia had been made.

DR. WYMAN: I think that is correct. This first set of films was not recorded in the protocol.

DR. FENNELL: The old record was lost; I did not know that any x-ray films were taken in the other hospital.

DR. WYMAN: Four days later there has been a startling change in the lungs; they now appear clear; the density in the right-upper-lung field and the other over-all density in the lung have disappeared largely if not entirely. The last examination was made two months later.

DR. BAKER: When she was an outpatient after discharge from the hospital?

DR. WYMAN: Probably; and we have none in the last entry. On the next set of films there is again an over-all patchy density in the lung fields that is not as homogeneous as that on the original set of films (Fig. 3). It seems to be more linear and patchy and more mottled, and the hilar shadows again appear very much more prominent than they did two months previously. I think the over-all increase in size of the chest is quite well seen. There is some fluid in the pleural space. The heart shadow is not sharply defined.

DR. BAKER: Is that a miliary type of density?

DR. WYMAN: It is larger than a miliary process, if miliary is considered to refer to the size of a millet seed, and the densities are somewhat more linear than a miliary process is. There seem to be interspersed patchy densities in addition to the linear changes, some of which appear to be engorged lymphatics and some to be vascular.

DR. BAKER: The lymphatics of the lung or along the bronchi?

DR. WYMAN: I should think it was running out along the vascular tree of the lung, but some peripheral lymphatics were engorged; we see this in cardiac decompensation.

DR. BAKER: She was not in outstanding decompensation at that time, as far as we know; she came into the Out-Patient Department.

DR. WYMAN: This picture is unusual for cardiac decompensation; these densities are more linear and sharply defined than the usual engorged vessel.

DR. BAKER: Will you comment on the enlarged spleen?

DR. WYMAN: I am sorry, I forgot to mention that. It is quite well seen and is definitely enlarged.

DR. BAKER: I think these x-ray examinations of the chest are important because they show a sort of conglomeration here two months after this woman was said to have had a pneumococcal pneumonia. They show that spotty diffuse infiltration at a time when according to the protocol she did not have many symptoms of congestive heart failure.

As a way of explaining these five unusual features in the history, the enlarged spleen, the fever, the abnormal blood protein, the kidney changes and the x-ray picture, I had considered the possibility that this was another case of valvular heart disease and unexplained fever, which always makes one think of subacute bacterial endocarditis. The unusual x-ray films tend to call my attention to something else. The Type-14 pneumococcus is said to be about the tenth most common finding in pneumococcal lobar pneumonia and is particularly frequent in children, but is not a common mouth inhabitant. These films, however, make one wonder whether the patient really had a pneumococcal pneumonia two months before admission and if so, how much it cleared up before she was discharged from the other hospital. I am not surprised that the physicians were concerned about tuberculosis and tried to rule that out — I suppose, by doing a skin tuberculin test, which one would expect to have been negative if this woman had had sarcoidosis. These films seem to me consistent with sarcoidosis. Do you think so, Dr. Wyman?

DR. WYMAN: I do not consider the two sets of films taken six months after the original examination consistent with sarcoidosis. I should think of an acute process that had cleared very rapidly in the course of four days.

DR. BAKER: That rapid clearing certainly would be unusual. That feature argues against such an explanation for this x-ray picture; but I found a case in which, in films taken a few days apart, there was remarkable clearing of pulmonary sarcoidosis.* I think the reappearance of this sort of picture two months later should make us think of that diagnosis in a woman who had an enlarged spleen and hyperglobulinemia.

What else could have produced such a readily palpable spleen in a woman with congestive heart failure? One possibility is the combination of con-

*This is an error, which was due to a typographic mistake in dating x-ray films and to failure to check the case protocol. (Longcope, W. T., and Fisher, A. M. Effect of Schaumann's disease upon heart and its mechanism. *Acta med. Scandinav.* 108:529-543, 1941.)

gestive heart failure and an asthenic build. I can remember feeling only one palpably enlarged spleen in congestive heart failure, and that was not verified at post-mortem examination. If the patient had subacute bacterial endocarditis as well as rheumatic heart disease, that would explain the splenomegaly and also the change in the serum globulin level, which may increase to a modest degree in subacute bacterial endocarditis. The mechanism of that is not clear. Such a hyperglobulinemia has been noted in sarcoidosis by several observers. If this woman had had sarcoidosis with enough pulmonary infiltration as well as heart disease, the terminal fever would have been quite in keeping. The fever is not an outstanding symptom of sarcoidosis unless there is marked activity and particularly pulmonary lesions. Judging from the impaired urea clearance, I can only conclude that this woman had definite renal insufficiency in the last few months of life. That would be difficult to explain on the basis of this premise of sarcoidosis. That disease does involve the kidneys, but rarely to the point of renal insufficiency.

Another more common possibility that might explain the feverishness and chest pain before the terminal admission, of course, is repeated pulmonary embolization and infarction, which the physicians must have considered during the first admission and for which Dicumarol administration was presumably begun, but it would be unusual for pulmonary infarcts to clear in the course of four or five days, would it not, Dr. Wyman?

DR. WYMAN: Yes. I should like to go back to the question of sarcoidosis. I do not see how sarcoidosis could produce these x-ray pictures; I cannot go along with that. I should have to consider pulmonary edema very strongly at that time. What else could do it I do not know; that is the only condition I can think of that would clear so quickly in the x-ray films.

DR. BAKER: Can you say that there was also congestive heart failure?

DR. WYMAN: The picture does not look quite typical of congestive heart failure. I am concerned about something else; I should make pulmonary congestion the major consideration, but I think there may have been something else as well.

DR. BAKER: I think this woman had rheumatic heart disease with congestive heart failure, that she died with posterior myocardial infarction and that she may have had either an associated sarcoidosis or multiple pulmonary infarcts.

DR. WYMAN: We have been interested in these miliary processes in the lungs; I patient who had a process not unlike this turned out to have amyloidosis. I suppose there is no chance of that condition in this case.

DR. BAKER: I thought of the possibility of amyloidosis in relation to the spleen, but the amyloidosis would have to have been primary. With primary amyloidosis, certainly, I should expect more albuminuria and a low serum protein rather than the relatively high protein reported.

CLINICAL DIAGNOSES

Acute posterior myocardial infarction.
Arteriosclerotic heart disease.
Congestive heart failure.
?Rheumatic heart disease.
Scoliosis due to old poliomyelitis.

DR. MYLES P. BAKER'S DIAGNOSES

Rheumatic heart disease, with congestive heart failure.
Myocardial infarction.
?Sarcoidosis.
?Multiple pulmonary infarctions.

ANATOMICAL DIAGNOSES

Subacute bacterial endocarditis, aortic and mitral valves.
Rheumatic endocarditis, chronic, aortic and mitral valves.
Coronary-artery disease with myocardial infarction, old.
Embolic occlusion of left anterior descending coronary artery.
Embolic glomerulonephritis.
Chronic pyelonephritis.
Healed infarcts of spleen and kidneys.

PATHOLOGICAL DISCUSSION

DR. FENNELL: The most interesting change was in the heart. It was about twice the normal size, weighing 550 gm., which is quite large for a woman of the size of this patient. On the aortic valve involving all three of the cusps were grayish-yellow vegetations, which varied in size from very minute up to 1 cm. in diameter. They had extended down on the left ventricular endocardium, and there were also vegetations on the mitral valve. This heart, I am sure, had been the seat of previous rheumatic infection. There was thickening and fibrosis of the valves, and some shortening of the chordae tendineae of the mitral valve.

Microscopically, the vegetations were typical of subacute bacterial endocarditis, with fibrin, platelets, leukocytes and easily seen clumps of bacteria, gram-positive streptococci. There was also some evidence of healing in that there were foci of calcification and some giant-cell changes in these vegetations. In the myocardium there was no evidence of the damage or changes one sees in bacterial endocarditis, but there was an old scar in the apex and considerable coronary-artery disease. In addition there was a loose thrombus in the anterior descending branch of the left coronary artery that microscopically looked like a fragment of vegetation in that it contained some calcification and several foci of bacteria. It is most unusual

in our experience for this to occur. There was no evidence of active rheumatic myocarditis. A number of sections of the myocardium gave no evidence of active rheumatic fever.

In the spleen there were old infarcts — I do not know how old they were but certainly old enough to have become converted partially into fibrous tissue. No evidence could be found of malaria, and there was no pigment, no fibrosis and no changes other than in the scars. The kidneys contained old scars and in addition microscopically showed old inactive pyelonephritis and, as might have been expected with bacterial endocarditis, embolic glomerulonephritis. The explanation of the pulmonary changes noted in the x-ray films was congestion and edema.

DR. WYMAN: That could not have been due to tiny emboli?

DR. FENNELL: We often see small thrombi or emboli in patients who have congestive heart failure, but we found none in this patient. I do not know how long this patient's disease had lasted. I suppose it must have started approximately a year before she died although from the anatomic standpoint I do not know how one could be certain of that. On looking at her chart, one can see that she had some swinging fever up to the time she was discharged after the first admission. Certainly, the disease can run this long a course, and I think it is likely that this was the explanation for her illness for one year. Of course, she had coronary-artery disease, and I think she actually died of congestive heart failure.

DR. JAVIER CORREA: Did the aorta show syphilitic aortitis?

DR. FENNELL: Grossly, it looked like syphilitic aortitis, but microscopically we could not find any signs of that disease.

CASE 39312

PRESENTATION OF CASE

A sixty-seven-year-old man came to the Emergency Ward because he had vomited blood.

The patient had been well until the evening before admission, when he passed a considerable amount of dark-red blood by rectum and continued to pass large quantities of blood to the time of admission. He had also vomited blood once during the night. There were no other symptoms.

The past history was noncontributory except that two years before admission he reported to the Out-Patient Department because of pain in the shoulder. At that time the hemoglobin was 20 gm., and the nonprotein nitrogen 50 mg. per 100 cc., and a phenolsulfonephthalein test showed 35 per cent excretion of the dye in one hour. A tentative diagnosis of angina pectoris was made, and the patient was advised to return but he was not seen again until the present admission. There was no history of a large alcoholic intake or jaundice.

Physical examination showed a well developed and well nourished but pale man. The heart and lungs were normal. The abdomen was soft and nontender. The spleen was palpable 4 cm. below the left costal margin, and the liver edge 2 cm. below the right costal margin. The rest of the examination was negative.

The temperature was 98°F., the pulse 110, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 cc. and a white-cell count of 32,500, with 92 per cent neutrophils. The serum nonprotein nitrogen was 82 mg. per 100 cc., and the prothrombin time 16 seconds (normal, 14 seconds). The sodium was 141 milliequiv., the chloride 103 milliequiv., and the potassium 4.7 milliequiv. per liter. A stool guaiac test was ++++.

In the hospital the patient was given five transfusions in about six hours. The pulse dropped to 96, and the blood pressure had stabilized at about 130 to 140 systolic, 80 diastolic. The skin was warm and dry. A gastrointestinal series demonstrated a small hiatus hernia, large esophageal varices, a normal duodenal cap and no gastric ulcers. There were no signs of renewed bleeding during the night, but the next afternoon the blood pressure dropped, the pulse rose, and the hemoglobin was 8.0 gm. per 100 cc. After a balloon tube had been passed and transfusions started, the patient was taken to the operating room, where a transthoracic, transesophageal ligation and plication of bleeding esophageal varices, as well as a repair of the hiatus hernia, were performed.

The immediate postoperative course was satisfactory, and there was no evidence of further bleeding. On the fourth postoperative day the serum total protein was 5.1 gm., the albumin 3.6 gm., the globulin 2.8 gm., the nonprotein nitrogen 47 mg., and the alkaline phosphatase 14.7 units per 100 cc.; the sodium was 135 milliequiv., the potassium 3.7 milliequiv., and the chloride 101 milliequiv. per liter. The cephalin flocculation was ++ in twenty-four and forty-eight hours, and the prothrombin time 16 seconds (normal, 14 seconds). A roentgenogram of the chest revealed some enlargement of the heart, apparently of the left ventricle. There was some linear atelectasis in both lower-lung fields.

On the tenth postoperative day the patient began to complain of crampy abdominal pain. Peristalsis was normal, and he was passing feces by rectum. Since the operation the temperature had been irregular and slightly elevated to 99.5°F., and the pulse steady at 85. Neither of these changed with the onset of abdominal pain. A plain film of the abdomen did not show any abnormal distention

of the bowel. The spleen was enlarged, and there was some lack of definition of structures of the posterior abdominal wall. During the next few days similar abdominal pain recurred from time to time but was unassociated with any change in clinical or laboratory findings. There was no fever or leukocytosis, and the bowels had moved well. On the sixteenth hospital day the patient complained of severe pain, which was steady and located in the midabdomen. The abdomen was more protuberant than before, and there was some poorly localized tenderness in all quadrants. There was shifting dullness; peristalsis was normal. The white-cell count was 15,500. A second plain film of the abdomen did not reveal abnormal distention of the bowel. He vomited once during the day, but later in the day felt better after an enema. During the next two days he was ambulatory but still complained of some intermittent lower abdominal pain. Two days later he complained of constant epigastric pain relieved only temporarily by 75 mg. of Demerol. He had continued to move his bowels; the stools were guaiac negative. On examination bowel sounds were fairly good; there was still dullness in the flanks. Late on this day the temperature rose to 100.5°F., and the pulse to 115. On the next day he appeared ill although his temperature and pulse were not elevated. The chest was clear. The abdomen was somewhat distended, with some dullness in the flanks. Peristalsis was absent. There was some tenderness to percussion over the right lower anterior portion of the chest. The liver edge was not palpable, but the spleen was felt 5 fingerbreadths below the left costal margin. The white-cell count was 17,900; the hemoglobin was 13.0 gm. per 100 cc. Later in the day pain increased, and the abdomen was more distended. There was evidence of more fluid; peristalsis was still absent, and there was rebound tenderness. On a diagnostic abdominal paracentesis 8 cc. of yellow, opalescent and nonodorous fluid was recovered that contained 600 white cells per cubic millimeter, 98 per cent of which were neutrophils. On the following day pain had continued, and ascites had increased. Another plain film of the abdomen was normal. A second abdominal paracentesis produced 1800 cc. of slightly bloody fluid. This contained 9100 cells per cubic millimeter, 8750 of which were red cells. On subsequent examination there was no localized tenderness, and peristalsis was normal. The temperature was 99°F., and the pulse 100. The white-cell count was 33,000, with 84 per cent neutrophils; a stool specimen gave a ++++ guaiac test. Several hours later an operation was performed.

Differential Diagnosis

Dr. Jacob Lerman*: On admission the spleen was felt 4 cm. below the left costal margin; on the twenty-first hospital day it was 5 fingerbreadths below the costal margin. Can someone tell me whether this means that the spleen had increased in size?

Dr. Edgar B. Taft: According to the record on admission the spleen was somewhat larger than it had been.

Dr. Lerman: The problem is twofold: to make a diagnosis of the original condition that this patient had and to determine the condition for which he was operated on. When I realized that he had polycythemia and that he was bleeding, I expected to find either a gastric or a duodenal ulcer; therefore, the finding of varices was unexpected. From the initial history I can assume that he had polycythemia and that everything else that followed was a complication of the polycythemia. He had lost considerable blood before admission so he must have had a high hemoglobin. He still had a hemoglobin of 11.5 gm. per 100 cc. on entry. Subsequently, with further blood loss and dilution, the hemoglobin went down to 8 gm. in spite of 6 transfusions. The original diagnosis of angina pectoris was probably correct because many patients with polycythemia have angina pectoris and may have congestive heart failure as well.

The varices, then, must be explained. How do esophageal varices develop in a patient with polycythemia? The two most likely explanations are cirrhosis — some of these patients have portal cirrhosis — and splenic-vein thrombosis, which in my opinion is more likely. The evidence for liver damage is slight. On two occasions the prothrombin time was reported to be normal. In spite of all the blood lost, the total protein was fairly good, with an albumin-globulin ratio of 1.3 and the cephalin flocculation was ++. All that, without any obvious evidence of jaundice or ascites on admission or soon after admission, argues against the presence of any serious cirrhosis.

When bleeding continued the patient was operated upon and varices were plicated. He was well for at least ten days after operation until generalized midabdominal pain occurred; the spleen was perhaps slightly more enlarged and a suggestion of ascites was noted in the x-ray films. There was no evidence of distended loops of bowel on x-ray examination at first, and there was no fever or leukocytosis, but by the sixteenth day, evidence of obstruction — more distention, diffuse tenderness and obvious ascites — appeared. The white-cell count went up to 15,500, and yet peristalsis was said to be good; the abdominal symptoms grew progressively worse, and ascites increased. Perhaps I should see the x-ray films now.

Dr. Joseph Hanelin: The gastrointestinal examination reveals definite esophageal varices. The spot films particularly show the large veins well. The film of the abdomen, in which the stomach is filled, demonstrates a generous spleen and a

*Associate physician, Massachusetts General Hospital.

liver only questionably enlarged. The stomach is not grossly abnormal, and the duodenum seems to be within normal limits. There is probably some retained material within the stomach. A series of plain abdominal films made over a three-week interval show what appears to be some progressive enlargement of the spleen. In the first plain film of the abdomen, one would be hard put to be certain that ascites was present, but in the last two films — possibly the last three films — one can see evidence of fluid, particularly in the pelvis; in the last film one notes considerable fluid within the abdomen, with much bulging of the flanks and obliteration of the normal psoas-muscle shadows. In none of these films do I see any clear-cut evidence of obstruction. The chest films do not contribute a great deal. The heart is only questionably enlarged, the diaphragm is elevated, and there are a few streaks of linear density at the bases that are either scars or zones of atelectasis.

Dr. Lerman: In the first few days that the gastrointestinal problem existed peristalsis persisted, ascites developed and distention progressed. The ascitic fluid was exudative and contained a small amount of blood. The character of the process in a patient with polycythemia is highly suggestive of the development of further thrombosis of the portal system, including the mesenteric radicles, resulting in paralytic ileus and peritonitis. It is difficult to understand why on the day before operation, after paracentesis, peristalsis returned and tenderness disappeared. The leukocytosis persisted, and apparently there was blood in the stool; both are consistent with mesenteric-vein thrombosis and a gangrenous bowel.

Another possibility is gangrenous gall bladder, suggested by severe epigastric pain and the tenderness over the anterior portion of the right side of the chest. If this had been a gangrenous gall bladder it would have to have perforated to produce the ascites, but the protocol clearly stated that the fluid was not infected and did not have the odor of fluid produced by a perforated viscus. One has to consider acute pancreatitis, but there does not seem to be enough evidence for this. The progressive increase in the spleen suggests torsion, but this is a more acute process and requires an emergency procedure.

In the presence of polycythemia a complicating tumor is not uncommon. In one reported series of patients with polycythemia the incidence of cancer was extremely high[1] — 10 to 15 per cent — so one must think of the possibility of an intra-abdominal tumor or metastases of an intra-abdominal tumor that caused partial abdominal obstruction.

On the whole, the symptoms can best be explained by thrombosis of the portal system with mesenteric thrombosis, resulting in gangrenous bowel and requiring surgical intervention; the diagnosis of the original condition is polycythemia and splenic-vein thrombosis.

Dr. Thomas H. Green, Jr.: The physicians on the Service, reasoning much as Dr. Lerman has, thought the primary diagnosis was polycythemia vera. We believed we were fortunate to have the record of the single outpatient visit, for at least we knew the patient had an elevated hemoglobin one year before admission. He never returned for follow-up studies. We believed the episode that brought him to the hospital represented bleeding esophageal varices, developing on the basis of splenic-vein thrombosis. In view of the poor renal function and the possibility of underlying liver disease we hoped not to have to operate on him, but when the varices bled again twenty-four hours later, it was necessary to go ahead with transthoracic ligation and plication. Postoperatively, he was well until about the eleventh day, when he began to suffer intermittent bouts of abdominal pain, which we were unable to diagnose definitely until nearly two weeks later. We considered throughout his course the possibility of mesenteric-vein thrombosis, a diagnosis that is at times notoriously difficult to make, because the thrombosis may progress very slowly and produce a benign clinical picture. Serial x-ray films of this patient's abdomen were normal except for slowly increasing ascites. Repeated stool guaiac tests were negative. Finally, when the ascites became marked enough, diagnostic paracenteses were done. On the last one, red cells appeared in the fluid, and simultaneously the stool became guaiac positive. This seemed to be conclusive evidence of mesenteric thrombosis.

Clinical Diagnoses

Mesenteric thrombosis, with gangrenous bowel.
Polycythemia vera.
Splenic-vein thrombosis, with bleeding esophageal varices.

Dr. Jacob Lerman's Diagnoses

Mesenteric-vein thrombosis, with gangrenous bowel.
Polycythemia.
Thrombosis of portal system.
Splenic-vein thrombosis.

Anatomical Diagnoses

Mesenteric-vein thrombosis, with infarction of segment of small bowel.
(Polycythemia.)

Pathological Discussion

Dr. Green: At operation there were several liters of serosanguineous peritoneal fluid. Beginning a few inches below the ligament of Treitz, the small bowel was involved in varying stages of infarction and gangrene for a distance of about a meter. The mesentery supplying this segment was markedly

edematous and thickened, and the veins were greatly distended. Resection of the involved bowel and mesentery was carried out, and thrombi could be seen plugging the veins in the portion of mesentery removed.

DR. TAFT: The specimen we received was a 90-cm. segment of small bowel, the middle third of which was dark red, congested and somewhat necrotic in appearance. Some of the veins in the mesentery had obvious gross thrombi, two of which were moderately adherent to the vein wall. This was a typical picture of a mesenteric-vein thrombosis, with necrosis of the bowel. This patient is still in the hospital; Dr. Green, perhaps you could tell us more about the postoperative course.

DR. GREEN: After this second episode of thrombosis we became quite concerned about further thrombotic manifestations and started him on Tromexan and Dicumarol to control that aspect of the clotting mechanism. Subsequently, the radiologists agreed to give spray radiation to reduce the platelets. Dr. Laurence Robbins informed us that he had never seen a polycythemia go on to further thromboses once radiation therapy had been started. We proceeded on that premise, and the patient has done very well since. The platelets, which were around 800,000, have dropped in three or four weeks to a normal of about 300,000; he has had no further thrombosis; the ascites is clearing and he is nearly ready to go home.

DR. LERMAN: What was the hemoglobin?

DR. GREEN: It was 11.0 gm. per 100 cc., and the white-cell count around 5000.

DR. KURT J. ISSELBACHER: Did the liver appear nodular at operation?

DR. GREEN: At laparotomy the liver was somewhat nodular. There may well have been some portal-vein thrombosis as well. However, the liver-function studies remained negative.

DR. DANIEL S. ELLIS: When I saw the patient about twelve hours before he was operated on, I believed the most likely diagnosis was mesenteric thrombosis but that there was not enough evidence of it to warrant exploration at that time. Within the next twelve hours, because the house staff gave him diligent attention and looked at him every three or four hours, we were able to make the diagnosis, to operate on him and to resuscitate him from a state that, twelve hours before, I did not think he could survive.

There is another patient in the hospital at the present time who has had portal hypertension and who after a shunt operation and splenectomy has developed a marked degree of polycythemia, and developed thrombosis of the subclavian vein. We are confronted with the same problem of treatment as we were with this man.

DR. TAFT: This patient is a typical example of those with polycythemia, who, according to Wintrobe,[2] frequently have hemorrhage from esophageal varices. At times the hemorrhage may be massive and may be associated with splenomegaly, as in this patient, and with hepatomegaly, but cirrhosis apparently is not too common a complication of this disease. Of course, as Dr. Lerman mentioned, thrombosis of the mesenteric vein is a frequent complication and is often mistaken for peritonitis and perforated duodenal ulcer, which these patients may have as well.

DR. MADAN M. SINGH: How frequently do you see so much ascites in mesenteric thrombosis?

DR. TAFT: I think one may assume that in this patient there was an element of possible portal-vein thrombosis, or at least obstruction of the portal vein as well, because I doubt if the small focus of mesenteric thrombosis with necrosis of the bowel, as this patient had, would produce such a massive ascites.

DR. ELLIS: How massive was it?

DR. GREEN: We withdrew 1800 cc. on the last tap. We have seen ascites occur before with necrosis of smaller segments of the bowel. When the bowel becomes gangrenous fluid accumulates rapidly.

DR. SINGH: It was on account of the excessive ascites that the question of hepatic-vein thrombosis was raised.

DR. ISSELBACHER: I think the diagnosis of hepatic-vein thrombosis was thought not likely because there was no jaundice and the liver was not enlarged.

DR. TAFT: The possibility of hepatic-vein thrombosis was discussed in the record, and it was pointed out that the liver was not enlarged and there was no jaundice, so that was discarded as being unlikely.

DR. SINGH: Gross jaundice is not frequent in hepatic-vein thrombosis.[3]

DR. TAFT: The 2 patients I have seen with hepatic-vein thrombosis were jaundiced.

REFERENCES

1. Videback, A. Polycythemia vera: course and prognosis. *Acta med. Scandinav.* 138:179-187, 1950.
2. Wintrobe, M. M. *Clinical Hematology.* Second edition. 862 pp. Philadelphia: Lea and Febiger, 1947. P. 592.
3. Thompson, R. B. Thrombosis of hepatic veins: Budd-Chiari syndrome. *Arch. Int. Med.* 80:602-615, 1947.

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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A SINGLE STANDARD

THE *Journal*, on March 19, 1953, published a paper on group practice with branch centers in a rural county, which had been presented by its author at a meeting of the Medical Care Section of the American Public Health Association. It described the experiences of a group that had been established in 1946 in rural Columbia County, New York.

This group, the Rip Van Winkle Clinic, has met with a firm and apparently growing opposition on the part of many of the physicians of Columbia County, who have been moved to express their criticisms in a strongly worded communication printed elsewhere in this issue of the *Journal*. The *Journal*, which accepted the original paper and now publishes the letter, is taking no part in this controversy. Its interest is in maintaining an open forum where all reasonable views may be aired, and in trying to support high, even if changing, principles in medical practice, regardless of cases.

Progress, it is perhaps safe to state, is a movement forward or a gradual betterment of things or conditions or ideals sometimes specifically defined as the "progressive development or evolution of mankind as a process." Progress always means change, but certainly change does not always mean progress. Differentiations must often be made between mere change, which may be entirely destructive, and progress, which has always a constructive goal ahead, even if the movement toward that goal involves damage to existing structures or customs or ways of life.

The science of medicine as well as its deployment is also in constant change; and change, unless very gradual, is a disturbing factor whether or not it represents progress. For rarely can new implements, new methods, new ideas be put into use without some loss of function and abandonment or destruction of the old.

The effort on the part of practitioners to keep up with the scientific advances in medicine is disturbing to personal equanimity as is all effort to meet constantly changing requirements. Efforts at bringing better medicine within the reach of ever-greater numbers require new ideas, new plans and new organizations, conspicuous among which have been prepayment or insurance plans and various experiments in group practice.

Many of these attempts, all of which are progressive in concept, have come to be accepted as representing real progress; some have proved to be abortive; others will be found to have failed because of poor design or poor organization or the emergence of selfish interests. One fundamental factor without which no organized effort deserves to succeed has been clearly stated in the communication from the physicians of Columbia County: "*. . . a group has the same responsibility and obligation to maintain medical ethics as does an individual practitioner.*"

FURTHER PROGRESS IN THE STUDY OF POLIOMYELITIS

As the epidemic peak of poliomyelitis approaches, two timely papers that consider various aspects in the control of the disease are presented in this issue of the *Journal*. The article by Siegel and Greenberg describes a study of the occurrence of poliomyelitis in households as the basis for determining the value of gamma globulin in its control; the Medical Progress report by Weller presents the advances achieved, as measured mainly by contributions of the past five or ten years.

The difficulties connected with the rational use of gamma globulin were recently the subject of editorial comment in the *Journal*[1]; most important is the inability to recognize the great majority of contagious cases of poliomyelitis and therefore the persons exposed to risk. Hence the necessity for relying on exposure to a known case within the family as one of the main indications for the administration of gamma globulin as a prophylactic. However, as Aycock and Eaton[2] pointed out in 1925, the evidence is strong that the majority of multiple cases within a family are from a common source.

Stimulated by the necessity of establishing a scientific basis upon which to make judgments, Siegel and Greenberg set about gathering further data that might serve as a partial guide for the distribution and application of gamma globulin. Although multiple cases were found to occur in about 1 out of 20 to 40 households in which a case of poliomyelitis had already occurred, the efficacy of gamma globulin administration is presumably halved because about 50 per cent of patients in the multiple cases manifested neurologic signs within five days of infection in a sibling. Consequently, the tendency for multiple infections within a family to have a common source, as indicated by the elapsed time between the onset of successive cases in the household, seriously limits the possibility of immunizing contacts of the first case. An unexpected finding was that the increased risk of clinically manifest infection after household exposure was proportionately greater from fifteen to thirty-four years of age than in the younger groups. The older the patient, the less likely he is to have suffered from an infection of common source and the more reasonable it is to give the injection. On the other hand cases in persons fifteen to thirty-four years of age constitute a relatively small proportion of multiple infections within the family and the medical profession and public are left with their dilemma for "the difference did not seem great enough to compensate for the lower incidence of clinical infection over fourteen years of age in deciding which group would benefit most from the limited supply of gamma globulin."

A notable stimulus to investigative effort has been the development of tissue-culture technics for propagation of the viruses of poliomyelitis as reported by Enders, Robbins and Weller in 1949[3] and 1950.[4] Modifications were subsequently made by others in the interests of progressive simplification and standardization of method. Strains of poliomyelitis virus have now been successfully propagated for many months in cultures of nonnervous human or monkey cells, and satisfactory complement-fixing antigens for each of the three antigenic strains can be prepared from fluids harvested from infected cultures.

Until recently little diagnostic assistance could be promised the clinician, but now, as Weller points out, tissue cultures can be employed for the isolation and identification of the three main types of poliomyelitis virus and for antibody assay in both diagnostic and epidemiologic studies. Thus Kibrick and Enders[5] have isolated poliomyelitis viruses from 95 per cent of a group of 39 patients with paralysis and from 64 per cent of a group of patients with signs of nonparalytic infection. It is interesting that in three of the four years studied to date one of the three main strains of viruses tended to predominate heavily over the other two during a particular season. Such observations may have important epidemiologic applications as the problem is further clarified, and they are clearly worth studying in the interests of working toward an effective vaccine.

According to Weller an effective vaccine will need to be polyvalent. Whether or not such a vaccine must contain only the three prototype strains

of virus recognized at present is a matter of speculation now and of study in the future.

References

1. Editorial. Gamma globulin in poliomyelitis prevention. *New Eng. J. Med.* 248:786, 1953.
2. Aycock, G. F., and Eaton, P. Epidemiology of infantile paralysis: relation between multiple cases in same family. *Am. J. Hyg.* 5: 724-732, 1925.
3. Weller, T. H., Robbins, F. C., and Enders, J. F. Cultivation of poliomyelitis virus in cultures of human foreskin and embryonic tissues. *Proc. Soc. Exper. Biol. & Med.* 72:153-155, 1949.
4. Robbins, F. C., and Enders, J. F. Tissue culture techniques in study of animal viruses. *Am. J. M. Sc.* 220:316-338, 1950.
5. Kibrick, S., and Enders, J. F. Unpublished data.

WORLD CONFERENCE ON MEDICAL EDUCATION

Medical education, having had a thorough overhauling by Abraham Flexner over forty years ago, is again to be critically reviewed. Such reforms must be periodic; progress toward an unattainable goal, represented by a hypothetical summit, is always over a series of plateaus, never by a constant grade; evolution is a matter of starts and stops.

Flexner's study of American medical schools was made in 1910 almost because of a popular demand, it was so long overdue in view of the rate at which medicine in general was then progressing. Many schools, even of university grade, were found hopelessly inadequate; many were closed as a result of the investigation, and the standards of most of the rest were raised and have remained ever since under the supervision of the Council on Medical Education and Hospitals of the American Medical Association.

The reforms of forty years ago are therefore still in effect, and it is safe to say that no low-grade schools of medicine are today accorded recognition in this country, if, indeed, any still exist. But again a reorientation is needed, not that medical education has actually deteriorated or is in any desperate need of reform, but that the subject with which it deals has been ever advancing, and education must review its own methods of operating and take stock of its own material if it is to keep up. For these forty years have witnessed unprecedented scientific, economic and social changes, and new methods of training, applied, perhaps, to different types of material, are necessary if education is not to be frozen in its tracks. Flexible and continually receptive minds must be trained on a broader base of understanding if the doctors of tomorrow are to keep within their view at least the concept of scientific progress as well as an appreciation of the social and economic difficulties that are attendant on the proper distribution of medical care.

To start somewhere near the beginning of any renaissance in medical education a new appraisal of the type and quality of medical-school graduates is essential even if the statement appears to reflect on the quality and training of some, at least, of today's practitioners. Such an appraisal leads back to the selection of the medical student himself, and the suspicion lingers that too much emphasis is now placed on the scientific grades acquired in college and not enough on the quality and character of the individual, although the four years during which the students are in college should give ample time and opportunity for their selection.

Versatility is a requisite in the successful practice of medicine whether the physician is of the tough breed of family doctor or a specialist in one of the pin-point ramifications of a specialty. To be well educated he must at least be aware of the progress that is being made in other lines than his own; he must practice preventive medicine whatever his field, he must be thoroughly imbued with the spirit of public health, and he must appreciate the economic difficulties with which the problem of the distribution of medical care is beset. The point of view of the physician must reflect his good citizenship. He must realize that the only constant in life is change, and that one of his main concerns is to help direct the advancing front of his profession into the most effective courses.

To further the accomplishment of these objectives and to spread them widely, the First World Conference on Medical Education will take place in London next month. It will be held under the auspices of the World Medical Association with the collaboration of the World Health Organization and with the Council for International Organizations of the Medical Sciences and the International Association of Universities participating — truly an imposing array. Sir Lionel Whitby, vice-chancellor of Cambridge University and Regius Professor of Physic, will be the president. Dr. Hugh Clegg, editor of the *British Medical Journal* and a seasoned

veteran of many a council chamber, is secretary of the Program Committee.

If nothing else materializes at this first meeting, at least forward-thinking educators of different countries will confer in the common language of intellectual and social communication, and will become acquainted with each other's problems and ways of reacting to them.

"GIANTS IN THE EARTH"

UNDER the title "Giants in the Earth" Ole Edvard Rölvaag, born the son of fishermen in the Norwegian north country, has written in a dramatic novel of the settling of the Dakota wheatlands by his own countrymen, transplanted like himself. His text is from the sixth chapter of *Genesis*, Verse 4:

> There were giants in the earth in those days; and also after that, when the sons of God came in unto the daughters of men, and they bore children to them, the same became mighty men which were of old, men of renown.

There are giants in the earth in these days also, of various statures and from different lands and circumstances of birth. Sometimes they come most vividly to mind in that sense of loss when the world loses them and the earth takes them again.

Like Rölvaag, a native of Norway, Marius Smith-Petersen exemplified all that the New World owes to its Scandinavian pioneers, except that more than the others he remained a living bridge between his old world and his new. Frank Lahey, an illustrious surgeon and a still greater leader, created a legend in surgery that will live long after him.

Each of these was in his way a giant, and in meeting their minds, in learning from their teaching and now in honoring their memories one may imagine himself as traveling the same high road, inspired by the same urgent necessity of getting the world's work done. Faith, also, comes with the reflection that each one's place will be filled; that the earth will feel the tread of giants still unborn.

Dr. John M. Todd, of Monongahela city, relates that a new section of bone has been re-produced, in place of a piece taken away by a surgical operation in a boy's jaw, and that new teeth are being developed from the new bone.

Boston M. & S. J., *August 3, 1853*

MASSACHUSETTS MEDICAL SOCIETY

MARIUS NYGAARD SMITH-PETERSEN

1886–1953

Marius Nygaard Smith-Petersen was born at Grimstad, near the southern tip of Norway, on November 14, 1886, the descendant of a line of Norwegian sailingship owners. His parents were Morten and Kaia (Ursin) Smith-Petersen. After a year's study in a Norwegian gymnasium he came to the United States at the age of seventeen and attended the West Side High School in Milwaukee from 1904 to 1906, then matriculated at the University of Chicago. A year later he transferred to the University of Wisconsin, from which he graduated as a bachelor of science in 1910.

In 1914 he received his medical degree at Harvard and after various internships engaged in the practice of orthopedic surgery in Boston, in association with the late Dr. Elliott G. Brackett. On September 1, 1917, he married Hilda Dickenson, of Fitchburg, Massachusetts, who, with their two sons and a daughter, survives him. Loyal to his native land he remained a citizen of Norway until 1924, when he became naturalized in this country.

Dr. Smith-Petersen's rise to prominence in the field of orthopedic surgery was inevitable for one so single-minded in his love of his profession, and so determined that the skills he had acquired should be put to the widest possible use. An assistant instructor in orthopedic surgery at the Harvard Medical School from 1920 to 1930, he became instructor in the latter year and was clinical professor from 1935 to 1946, when he retired from formal teaching. In 1946 he retired also from his position as chief of the Orthopaedic Service at the Massachusetts General Hospital, which he had filled with such distinction since 1929.

He was a member of the International Society of Orthopaedic Surgeons; the American Orthopaedic Association and the American Academy of Orthopaedic Surgeons, of which he was president in 1943; and of the New England and Boston Surgical societies. From 1942 to 1945 he was consultant to the Surgeon General of the Army.

His impressive list of honors included an honorary degree from the University of Oslo in 1946 and membership in the Norwegian Surgical Society; the Grand Cross of the Royal Norwegian Order of St. Olaf, conferred in 1947; honorary membership in the British Orthopaedic Association and fellowship in the Royal Society of Medicine; honorary member-

ship in the French Academy of Orthopaedic Surgery, the Italian Society of Orthopaedic Surgery and Traumatology, the Royal Medical Society of Edinburgh and the Canadian Orthopaedic Association.

Dr. Smith-Petersen's fame, so far as one may be interested in such a measure of a man, will rest on the bold and successful attacks that he made on the intricate problems of his special field in surgery. His true greatness, to those who knew him, is a matter of more personal attributes.

It is a matter of the gentleness, the simplicity and the spirit of dedication with which he accepted the burdens of so many people. It is a matter of the esteem and loyalty that he inspired in the pupils and associates who surrounded him during the thirty years of his professional leadership. It is a matter of the affection of his many life-long friends. It is part of the quality that made him put the needs of his hospital above any personal considerations and led him to give to his native country a professional service and a personal devotion that were responsible for his characterization as Norway's foremost ambassador in the United States.

DEATH

ALLEN — Edward C. Allen, M.D., of Newton, died on July 14. He was in his thirty-ninth year.

Dr. Allen received his degree from Tufts College Medical School in 1939. He was chief anesthesiologist, Faulkner Hospital, and was formerly a member of the staff of the Lahey Clinic. He was a member of the American Society of Anesthesiologists, Inc., and a fellow of the American Medical Association.

He is survived by his widow, two sons, his mother, four sisters and four brothers.

CORRESPONDENCE

REGARDING THE RIP VAN WINKLE CLINIC

To the Editor: On March 19, 1953, the *New England Journal of Medicine* published an article entitled "Group Practice with Branch Centers in a Rural County," by Dr. Caldwell B. Esselstyn. Since this article contains many statements that convey erroneous impressions regarding past and present medical practice in Columbia County, the undersigned respectfully request publication of this letter.

From this article one would gain the impression that, medically speaking, Columbia County has been a backward community. The hospital in Hudson, New York, now the Columbia Memorial Hospital, was incorporated in 1889 and received its first patient in 1893. In 1900 a training school for nurses was established. This training school is still in operation. A gradual expansion occurred so that by 1924 the bed capacity was 100. In 1943, three years before the Rip Van Winkle Clinic was established, the Hospital Board of Trustees appointed a building committee to consult with Dr. Claude W. Munger, of New York City. At that time definite plans were made, and in 1945 approximately $500,000 was raised for the Building Fund. Owing to steel shortages and increased costs, the actual building project was delayed until 1950. In a second campaign in 1951 about $450,000 was raised. In March, 1953, the new $2,000,000 addition and reconstruction program was completed, increasing the bed capacity to 150. From Dr. Esselstyn's article the conclusion might be reached that the new addition was built chiefly through the efforts of the Rip Van Winkle Clinic. During the Building Fund Campaign the entire staff of the Rip Van Winkle Clinic pledged a combined total of $1,000, or $100 each, whereas the remaining 30 doctors in the County pledged $88,350, or an average of $2,945 each. Furthermore, at the time of the campaign in 1951, Dr. Esselstyn was actively soliciting local industry to obtain funds for his clinic.

The practice of medicine has been progressive in Columbia County. For over thirty years an affiliation with the Bender Laboratory, of Albany, New York, afforded complete laboratory and pathology service. Such an affiliation was terminated only after the services of a full-time pathologist had been obtained. Electrocardiographic service was established in 1932. Over twenty years ago, through the full co-operation of the Columbia County Medical Society, a county health unit was established. This unit has been maintained with a full-time health officer, veterinarian, sanitary inspector and nursing staff. At the time the Rip Van Winkle Clinic was established in 1946, there were on the hospital staff the following members certified by the appropriate boards: 3 general surgeons, 1 ophthalmologist, 1 otolaryngologist and 1 roentgenologist. In addition there were 2 board-eligible internists and a well trained obstetrician. All these doctors were residents of Columbia County and rendered full-time medical service. Through the Bender Laboratory affiliation, a blood bank was established at the hospital, a service that has been active and available for the past six years. The city of Hudson is located only 32 miles from the Albany Medical School, whose faculty has been, and still is, employed for consultations. Many of these consultant services have been rendered without charge.

Dr. Esselstyn states that the Rip Van Winkle Clinic is made up of 17 doctors. He fails to indicate, however, that only 8 of this group are in residence in the County. This number includes members of the group who operate the branch offices. The remaining 9 members make infrequent appearances. In an emergency such consultants cannot reach the community any faster than consultants whose services have been enlisted by the other doctors of the County for many years.

Fee schedules in Columbia County have always been modest, and all the doctors have given considerable free medical care. Specialists in the County, not connected with the Clinic, use Blue Shield and Workmen's Compensation as the index for fees but frequently honor other types of insurance in which the fee schedule is lower. Although no means test may ever have been applied by Dr. Esselstyn, the services of a bill collector are employed. It should be noted that the provision for supplying medical services at a cost 90 per cent of the people can afford is made possible through the rapid growth of medical care insurance, rather than through any efforts on the part of the Rip Van Winkle Clinic.

Dr. Esselstyn mentions the establishment of a cancer detection center on February 13, 1947, but neglects to state that on February 7, 1947, at a meeting of the Comitia Minora of the Columbia County Medical Society, held at his request, he sought the approval of the Committee for a cancer detection center to be established at his office. The Committee was in favor of such a center at the hospital but did not approve the establishment of a cancer detection center in any doctor's office. Rules of the American Cancer Society and the American College of Surgeons required approval by the County Medical Society before such a center could be established. These rules further suggested that whenever possible the centers should be located in hospitals. On February 8, 1947, the day after the Committee meeting, because of the adverse action of the Committee, Dr. Esselstyn told a member of the Committee that he was going to drop the matter. On February 18, 1947, at a meeting of the general staff of the hospital, Dr. Esselstyn announced that the cancer detection center at the Rip Van Winkle Clinic had held its first session five days previously. Either through an oversight or through falsification of the application for approval, the American College of Surgeons carried this center on its "Approval Lists" until the lack of approval of the County Society was called to its attention. Subsequently, the designation was changed from "Cancer Detection Center" to "Cancer Diagnostic Clinic," apparently as a subterfuge to obtain approval by the American College of Surgeons. County Medical Society approval was not required for a diagnostic clinic.

To obtain funds from the American Cancer Society, a detection center must submit project application blanks giving certain information. The signature of the president of the County Medical Society on such a blank would imply that the County Society had approved the application and operation of the center. Such an unfilled blank accompanied by a letter from Dr. Esselstyn was sent to the President of the Columbia County Medical Society in 1947. The letter requested the President's signature on the blank "in order that the American Cancer Society may know

that the project is being carried on by legitimate members of the profession."

In 1948 considerable pressure was put on the Columbia County Medical Society by the Medical Society of the State of New York to approve the Cancer Detection Center at the Rip Van Winkle Clinic. After several conferences, however, the action of the Columbia County Medical Society in this matter was upheld by the Council Committee on Public Health and Education of the Medical Society of the State of New York. A cancer detection center at the hospital, operated by the Columbia County Medical Society and approved by the American College of Surgeons, is now in its sixth active and successful year of operation.

Dr. Esselstyn states, "Among our errors was the attempt to include in our group two general practitioners with large practices." The original resident group consisted only of the director, his surgical assistant, a practitioner in Hillsdale and these 2 men. He further states, "The only method of reimbursement acceptable to these men was a percentage of the funds collected for their individual accounts." Both these men have signed this letter and they state that a salary was never suggested and that they contributed 30 per cent of their earnings to the Clinic. Since they are conscientious workers, they naturally did not have time for two-hour or three-hour luncheon conferences, preferring to give that time to their patients. Dr. Esselstyn states, "Charts could not be maintained," which is interesting since he, himself, at one time was about 600 charts behind at the hospital. This record delinquency covered a period of about five years. He also states, "Here was symptomatic medicine carried on with great intensity." The fact that these 2 men have large practices does not imply that they are superficial in their work. They are highly rated as intelligent and cautious practitioners. One of these men is a fellow of the American College of Physicians and has been, in fact, the personal physician to Dr. Esselstyn, himself, and to members of his family. During the first sixteen months of operation there were only 4 of the so-called fortnightly meetings that these 2 men "missed more often than not." They left the Clinic voluntarily, leaving Dr. Esselstyn much concerned and disappointed. Seven other doctors and a dentist, who were residents of the County, have left this clinic.

In 1948 Dr. Esselstyn was summoned to appear before the Board of Censors of the Columbia County Medical Society because of a headline feature article regarding the Rip Van Winkle Clinic that had appeared in a local newspaper. He appeared before the Board of Censors accompanied and represented by legal counsel. Dr. Esselstyn was censured, and the Columbia County Medical Society accepted his written apology in an open meeting.

A year ago approval of the Columbia County Medical Society was sought so that the Rip Van Winkle Clinic could be included in a television program concerning cancer. This program was sponsored by the American Cancer Society. Approval was not granted since it was thought that the Cancer Detection Center at the hospital could be used just as effectively. It has also been necessary to block other attempts at advertising.

Recently, a physician with a large practice in Germantown, New York, 10 miles south of Hudson, moved away. He obtained a young physician in resident training at the Albany Hospital to assume the responsibilities of his practice in July of this year. The dean of the Albany Medical College tried to discourage this young physician from locating in Germantown, presumably at the suggestion of Dr. Esselstyn, whose clinic plans to open a branch office there. It appears that Dr. Esselstyn desires to "attract well trained, young physicians to a rural area" only if they are to be associated with him.

Dr. Esselstyn obviously aims to become the czar of medicine in Columbia County. He has available to him funds from the Rip Van Winkle Foundation, which receives contributions, income-tax deductible, to aid him in the competitive practice of medicine and to help him obtain his goal. It is for these reasons that the Clinic has "been received with suspicion."

The reactions herein expressed are not only our own but also those of many of the physicians in the surrounding counties who share and appreciate our position. Most of them have read the article and heartily agree that a reply must be made. The doctors "who are not members of the group" have nothing against group practice. It is strongly felt, however, that *a group has the same responsibility and obligation to maintain medical ethics as does an individual practitioner.*

Signed,
H. G. Henry, M.D., Germantown, New York
Leroy Holbert, M.D., Kinderhook, New York
E. A. Jacobs, M.D., Hudson, New York
H. O. Little, M.D., Hudson, New York
Ralph F. Spencer, M.D., Hudson, New York
Gene S. Rogati, M.D., Valatie, New York
Oscar Wilcox, Jr., M.D., Chatham, New York
Joseph P. Gold, M.D., Hudson, New York
Elah C. Bliss, M.D., Hudson, New York
Roger C. Bliss, M.D., Hudson, New York
Heinz Salm, M.D., Hudson, New York
John Dardess, M.D., Chatham, New York
H. J. Noerling, M.D., Valatie, New York
Rosewell Shaw, M.D., Stottville, New York
John L. Edwards, M.D., Hudson, New York
Robert H. Little, M.D., Hudson, New York
Lawrence J. Early, M.D., Hudson, New York
Algird F. White, M.D., Philmont, New York
Harold Levine, M.D., Hudson, New York
Carl G. Whitbeck, M.D., Hudson, New York
E. F. Urba, M.D., Kinderhook, New York
R. L. Bowerman, M.D., Copake, New York
Leonard M. Niesen, M.D., Hudson, New York
Helen M. McEvoy, M.D., Hudson, New York
A. F. McEvoy, M.D., Hudson, New York

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

American Pocket Medical Dictionary: A dictionary of the principal terms used in medicine, nursing, pharmacy, dentistry, veterinary science, and allied biological subjects. Nineteenth edition. 16°, cloth, 639 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1953. $3.75.

This small well known medical dictionary was first published in 1898 and is now in its fifty-fifth year. The text has been revised, and obsolete terms have been eliminated. Many of the tables have been rewritten, and new tables on bones and veins included. These tables appear in their proper order in the alphabetical arrangement of the words. The volume is compact and should prove valuable to physicians, librarians and other interested persons.

Einführung in die Encephalographie (Pneumenzephalographie). By Dr. Med. Habil. Otto Schiersmann, professor of neuropsychiatry, and physician-in-chief, Krankenhauses Bethesda, Wuppertal-Elberfeld. Second revised edition. 4°, cloth, 135 pp., with 184 illustrations. Stuttgart: Georg Thieme, 1952. DM 36.- (Distributed by Grune and Stratton, New York; *Archiv und Atlas: der normalen und pathologischen Anatomie in typischen Röntgenbildern, Ergänzungsband 64*).

This second edition of an atlas on encephalography has been revised and brought up to date. The text is divided into two parts: general and special. The general part is divided into anatomy and physiology and the use of the x-ray. The special part discusses the importance of the encephalogram, its relation to pathologic processes, the boundary between normal and pathologic pictures, and the encephalogram in various diseases. There is a comprehensive bibliography and a good index. The publishing is excellent. The atlas should be in all collections on the subject.

The Esophagus and its Diseases. By Eddy D. Palmer, M.D., lieutenant colonel, Medical Corps, United States Army; chief, gastrointestinal section, Walter Reed Army Hospital, and consultant in gastroenterology to the Surgeon General. 8°, cloth, 553 pp., with 95 illustrations by Phyllis Anderson. New York: Paul B. Hoeber, Incorporated, 1952. $15.00.

This special work discusses in detail the anatomy and diseases of the esophagus. The literature has been reviewed, and lists of references are appended to the chapters. The book is well illustrated and well published. This good reference source should be in all medical libraries.

The Essentials of Medical Diagnosis: A manual for students and practitioners. By Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P. (Lond.), extra physician to H.M. the Queen and consulting physician to St. Bartholomew's Hospital; and A. E. Gow, M.D., F.R.C.P. (Lond.), consulting physician, St. Bartholomew's Hospital. Second edition. Revised with the assistance of Ronald Bodley Scott, M.A., D.M. (Oxon), F.R.C.P. (Lond.), physician to H.M. Household and assistant physician and senior demonstrator of practical medicine, St. Bartholomew's Hospital. 12°, cloth, 462 pp., with 23 plates, 22 figures and 5 charts. Baltimore: Williams and Wilkins Company, 1953. $6.00.

The first edition of this manual was published in 1928. This new edition has been carefully revised in every section, and the chapters on the blood, jaundice, the liver and the urinary system have been rewritten. There is a comprehensive index. The printing was done in Great Britain.

Your Health, Sir! By Miriam Lincoln, M.D. 12°, cloth, 211 pp. New York: Harper and Brothers, 1953. $2.75.

This book, written for the laity, discusses specifically the health problems common to men. The ordinary disorders and conditions are described in an easy manner. The final chapter is devoted to the subject of medical writing for the layman. The book is well published.

Headaches: Their nature and treatment. By Stewart Wolf, M.D., professor of medicine and head, Department of Medicine, University of Oklahoma School of Medicine; and Harold G. Wolff, M.D., professor of medicine (neurology), Cornell University Medical College. 12°, cloth, 177 pp., with 7 illustrations. Boston: Little, Brown and Company, 1953. $2.50.

In this book written for the general public, the authors have combined their experience of over twenty-five years in the practice of neurology, and discuss the various types of headache and their care and treatment. The small volume is suitable for a collection of medical books for the laity.

Visceral Circulation. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. Assisted by Margaret P. Cameron, M.A., A.B.L.S., and Jessie S. Freeman, M.B., B.S., D.P.H. 8°, cloth, 278 pp., with 72 illustrations. Boston: Little, Brown and Company, 1953. $6.50. (A Ciba Foundation symposium.)

The Ciba Foundation, an international center opened in June, 1949, has fostered 18 international symposiums, mostly concerned with steroid hormones. The present volume is the fourth general book to appear and contains all the papers and discussions of a symposium in which representatives from eight countries participated. The text is divided into four parts, as follows: visceral vascular architecture; general factors in blood-flow regulations; regional-flow circulation; and interaction of general and visceral circulation. This small volume, which is well published, should be in all collections on the circulatory system.

Atlas of Medical Mycology. By Emma Sadler Moss, B.M., M.D., director, Department of Pathology, Charity Hospital of Louisiana of New Orleans, and clinical professor of pathology, Louisiana State University School of Medicine; and Albert Louis McQuown, B.M., M.D., pathologist, Our Lady of the Lake Sanitarium, Baton Rouge, Louisiana, and clinical assistant professor of pathology, Louisiana State University School of Medicine. 4°, cloth, 245 pp., with 248 illustrations. Baltimore: Williams and Wilkins, 1953. $8.00.

This atlas is based on a series of exhibits prepared for medical conventions, demonstrations and lectures as part of a training program for resident physicians, students and medical technologists. The various fungi of medical importance are well illustrated and described. There are special chapters on methods, immunology, contaminants and culture mediums. The text concludes with a glossary and a formulary. There is a good index, and the book is well published. It should be in all collections on parasitology.

A Short Practice of Surgery. By Hamilton Bailey, F.R.C.S. (Eng.), F.I.C.S., F.R.S.E., senior surgeon, St. Vincent's Clinic and the Italian Hospital; and R. J. McNeill Love, M.S. (Lond.) F.R.C.S. (Eng.), F.I.C.S., surgeon, Royal Northern, Mildmay Mission, and Metropolitan Hospitals, consulting surgeon, City of London Maternity Hospital, consulting surgeon, Potter's Bar Hospital, associate for general surgery, West End Hospital for Nervous Diseases, member of Council and Court of Examiners, Erasmus Wilson Demonstrator, and Hunterian Professor, Royal College of Surgeons. With pathological illustrations by L. C. D. Hermitte, M.D., Ch.B. (Edin.), pathologist, Royal Infirmary, Sheffield. Ninth edition. 8°, cloth, 1254 pp., with 1234 illustrations. Baltimore: William and Wilkins, 1953. $12.50.

This standard English book, first published in 1932, has gone through 16 printings of 9 editions. The text has been thoroughly revised, and many chapters rewritten; a large number of illustrations have been added. There is a good index, and the publishing is excellent (the printing was done in Great Britain).

The Wechsler-Bellevue Scales: A guide for counselors. By C. H. Patterson, Veterans Administration Center, Fort Snelling, St. Paul, Minnesota. 8°, paper, 146 pp., with 8 tables. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 148, *American Lecture Series.*)

This monograph represents a detailed revision and expansion of a mimeographed manual prepared in 1948 by the Veterans Administration Regional Office in Minneapolis. It is intended as a guide to occupational counselors in determining the mental states of patients coming under their observation. The text describes the nature of the scales, the reliability and validity and the methods of administering tests and how to report the results. There are chapters on use in clinical diagnosis, measurements of mental deterioration, the application of the scales in aptitude measurements and a description of short forms of the scales. An extensive bibliography and a good index are appended to the text. The monograph should be in all collections on mental disorders.

Acute Renal Failure: Including the use of the artificial kidney. By John T. MacLean, M.D., F.R.C.S.(C), assistant urologist, Royal Victoria Hospital, director of urology, Queen Mary's Veterans Hospital, Department of Veterans Affairs, and demonstrator in surgery, McGill University Faculty of Medicine, Montreal, Canada. 8°, cloth, 114 pp., with 27 illustrations and 5 colored plates. Springfield, Illinois: Charles C Thomas, 1952. $6.50.

Dr. MacLean discusses acute renal failure in its various aspects, including its causation, physiology, diagnosis and treatment. There is a special chapter on dialysis with the artificial kidney. The small book is well published and should be in all collections on diseases of the kidney.

Clinical Investigation: A manual for practitioners and students. By E. H. Stokes, M.D., Ch.M. (Sydney), lecturer in clinical medicine, University of Sydney. With a foreword by G. E. Beaumont, M.A., D.M., F.R.C.P., D.P.H., physician to the Middlesex Hospital. 8°, cloth, 628 pp., with 344 illustrations. Sydney: Angus and Robertson, 1953. £5-5-0.

The text of this new book on clinical diagnosis is arranged by the various systems of the body. There are also chapters on case recording, general appearances in diseases and errors and pitfalls in diagnosis. There is a good index, and the publishing is excellent (the printing was done in Australia).

Comroe's Arthritis and Allied Conditions. Edited by Joseph Lee Hollander, M.D. Fifth edition. 8°, cloth, 1103 pp., with 399 illustrations. Philadelphia: Lea and Febiger, 1953. $16.00.

This standard work, continued since Dr. Comroe's death in 1945 by a group of well known physicians, has been completely revised and rewritten, and the text brought up to date. Lists of references are appended to the chapters, and there is a good index. The publishing is good, and the book should be in all collections on the subject.

Endocrine Treatment in General Practice. Edited by Max A. Goldzieher, M.D., and Joseph W. Goldzieher, M.D. 8°, cloth, 474 pp., with 19 illustrations. New York: Springer Publishing Company, Incorporated, 1953. $8.00.

This new book is the joint work of 21 specialists. The text is divided into five parts: disorders related to age; disorders of metabolism and nutrition; disorders of organ system; disorders of resistance and neoplastic diseases; and hormone preparations, currently available. There is a good index, and the printing is excellent, on a lightweight paper. The book should be in all collections on endocrinology.

Microbiology and Pathology. By Charles F. Carter, M.D., director, Carter's Clinical Laboratory, Dallas, Texas, and consulting pathologist, St. Louis Southwestern Railway Hospital, Texarkana, Arkansas; and Alice L. Smith, M.D., instructor in microbiology and pathology, Parkland Hospital School of Nursing, Dallas, Texas, assistant professor of pathology, Southwestern Medical College of the University of Texas, and consulting pathologist, Children's Medical Center, Dallas, Texas. Fifth edition. 8°, cloth, 847 pp., with 260 illustrations. St. Louis: C. V. Mosby Company, 1953. $5.50.

The authors have revised this standard textbook to bring the text up to date. Much of the material has been rewritten and rearranged. New material includes sections on the inhibition or destruction of bacteria by chemical agents, disinfection and sterilization, viruses and rickettsias; also, considerable material has been added to many of the chapters on pathology. Lists of questions for review purposes and short bibliographies are appended to the various chapters. The volume concludes with a glossary and a good index. The publishing is excellent, and the book should be in all medical libraries for reference purposes.

Letters to a Doctor's Secretary. By Anna Davis Hunt. 12°, paper, 75 pp. Rutherford, New Jersey: Medical Economics, 1952.

This small book presents, in a series of letters suggestions for general efficiency as a physician's secretary.

On the Social Frontier of Medicine: Pioneering in medical social service. By Ida M. Cannon. 8°, cloth, 273 pp. Cambridge: Harvard University Press, 1952. $4.75.

Miss Cannon is well qualified by training and experience to tell the story of the development of the Social Service Department of the Massachusetts General Hospital from its beginning to the present. She worked in the department for thirty-nine years, and for thirty-one years as its chief. She was long associated with the late Dr. Richard C. Cabot and relates the story of his persistent efforts to establish hospital social service on a sound footing. The text is divided into three parts: the background; pioneering; and the fruits of experience — in the last part Miss Cannon discusses the subject in its present-day light. The text is written in a pleasant style, and the chapters are documented with lists of references. The book should be in all medical and sociologic libraries.

Introduction to the Rorschach Technique: Manual of administration and scoring. By Robert M. Allen, M.D., professor of psychology, Department of Psychology, University of Miami. 8°, paper, 126 pp., with 16 illustrations. New York: International Universities Press, Incorporated, 1953. $3.00.

This manual is based on fourteen years of work and study with the Rorschach psychodiagnostic ink-blot test. The text is divided into three parts: theory and method; scoring symbols; and concepts. There is a bibliography of 53 references, as well as author and subject indexes.

Guide for National Studies of Nursing Resources. By Margaret G. Arnstein, R.N., M.P.H., chief, Division of Nursing Resources, United States Public Health Service, and nursing consultant, World Health Organization. 8°, paper, 36 pp., with illustrations. Geneva: World Health Organization, 1953. $0.20. (*Bulletin of the World Health Organization*, Supplement 7.)

This guide has been devised to assist nations in the study of their own nursing services in their broadest aspects, including all types of service and personnel.

Surgical Applied Anatomy. By Sir Frederick Treves, Bt. Revised by Lambert Charles Rogers, V.R.D., M.D., M.Sc., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S., professor of surgery, University of Wales, director of surgical unit, Cardiff Royal Infirmary, surgeon, United Cardiff Hospitals, surgical consultant to the Royal Navy, and member of Council, Royal College of Surgeons of England. Twelfth edition. 16°, cloth, 590 pp., with 206 illustrations. Philadelphia: Lea and Febiger, 1953. $6.50.

The first edition of this standard manual was published in 1883, and the small book has been issued continuously to the present. This new edition has been revised, and the material brought up to date. The printing was done in Great Britain. Seventy years of consecutive use speaks well for the value of the small book.

Amebiasis: Pathology, diagnosis and chemotherapy. By Hamilton H. Anderson, M.D., professor and chairman of the Department of Pharmacology and Experimental Therapeutics, the School of Medicine, University of California Medical Center, San Francisco, California, and dean of the medical faculty, American University of Beirut, Beirut, Lebanon, 1950–1951; Warren L. Bostick, M.D., associate professor of pathology, Department of Pathology, the School of Medicine, University of California Medical Center, San Francisco, California; and Herbert G. Johnstone, Ph.D., professor of parasitology and Mycology Section of the Department of Medicine, the School of Medicine, University of California Medical Center, San Francisco, California. 8°, cloth, 431 pp., with 50 illustrations and 25 tables. Springfield, Illinois: Charles C Thomas, 1953. $11.50.

In this monograph the authors discuss thoroughly the various aspects of amebiasis and review critically the pertinent literature on the subject. Bibliographies are appended to the various chapters, and there are extensive indexes of authors and subjects. The publishing is good; the book is recommended for all medical libraries.

Fanconi and Wallgren's Textbook of Paediatrics. Edited by W. R. F. Collis, M.A., M.D., F.R.C.P., F.R.C.P.I., D.P.H., lecturer in pediatrics, Dublin University, physician, National Children's Hospital, and director, Department of Paediatrics, Rotunda Hospital, Dublin. Translator and co-editor, E. Kawerau, M.B., M.Sc., A.R.I.C., senior lecturer in chemical pathology, St. Mary's Hospital, London. 8°, cloth, 1104 pp., with 441 illustrations and 5 tables. New York: Grune and Stratton, 1952. $19.50.

This new treatise on pediatrics is the joint work of 16 foreign specialists, principally from Europe. The well and the sick child are discussed in 33 chapters, covering the whole field of pediatrics. This is a practical book based upon personal experience and does not consider the literature on the various subjects. The book was originally published in German under the title of *Lehrbuch der Pädiatrie* and has been translated for English readers. There is a good index, and the publishing is excellent. (The printing was done in Great Britain.)

Problems of Infancy and Childhood: Transactions of the Sixth Conference, March 17 and 18, 1952, New York, New York. Edited by Milton J. E. Senn, M.D., Sterling Professor of Pediatrics and Psychiatry, Yale University School of Medicine. 8°, cloth, 160 pp. New York: Josiah Macy, Jr., Foundation, 1953. $2.50.

This conference discussed the emotional development and individual tendencies in the first year of life and excessive crying in infants as a family disease. A brief review of World Health Organization activities is presented. All the conferences of the Josiah Macy, Jr., Foundation should be in medical libraries.

Problems of Consciousness: Transactions of the Third Conference, March 10 and 11, 1952, New York, New York. Edited by Harold A. Abramson, M.D., associate physician for allergy, Mount Sinai Hospital, New York. 8°, cloth, 156 pp., with 6 figures and 7 tables. New York: Josiah Macy, Jr., Foundation, 1952. $3.25.

Twenty-five physicians and scientists attended this conference, where papers were read on consciousness and metabolism of the brain, hypnotic phenomena, and experimental variations of consciousness.

Metabolic Interrelations: With special reference to calcium: Transactions of the Fourth Conference. Edited by Edward C. Reifenstein, Jr., M.D., director, Oklahoma Medical Research Institute and Hospital, Oklahoma City, Oklahoma. 8°, cloth, 262 pp., with 50 illustrations and 16 tables. New York: Josiah Macy, Jr., Foundation, 1952. $4.50.

This fourth conference was attended by 29 physicians and 20 papers were presented on the calcium metabolism of bone and related tissues.

Collegiate Education for Nursing. By Margaret Bridgman. 8°, cloth, 205 pp. New York: Russell Sage Foundation, 1952. $2.50.

Dr. Bridgman in this report surveys the present and anticipated state of nursing education. The topics discussed include the critical deficiency in nursing services, the hospital school, the relation of education to study, and the baccalaureate curriculum in its various aspects. The book should be in all collections on nursing.

(*Notices on page xi*)